



# The American Journal of Medicine

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## Penicillin Therapy of Scarlet Fever and the Streptococcus Carrier\*

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SINCE its development, penicillin has been widely used as a therapeutic agent in numerous diseases. Its usefulness is now generally considered to be limited to diseases produced by the gram-positive organisms, *Neisseria*, spirochetes, fusiforms of Vincent, *Streptobacillus moniliformis* and a few others. It has been found to be highly effective against the group A hemolytic streptococci. Cases of its effectiveness in streptococcal infections after failure with sulfonamides have been described,<sup>6</sup> and comparisons of penicillin and the sulfonamides have been made on numerous occasions.<sup>1,8,11</sup> No direct study of the effect of penicillin on group A hemolytic streptococci known to be specifically resistant to the sulfonamides, however, has yet appeared.<sup>2</sup>

Attempts to evaluate proper and adequate doses for the various diseases susceptible to penicillin therapy have been made.<sup>13</sup> Plummer and his associates studied the specific effect of intramuscular administration of penicillin in hemolytic streptococcal pharyngitis and tonsillitis. They found a temporary suppression of positive cultures using 15,000 units every four hours but noted that relapses of both cultures and symptoms occurred if administration of the

drug was discontinued in less than six days. They also found that sulfadiazine reduced the number of organisms in nose and throat cultures but only during the period of exposure to the drug. This effect of sulfadiazine has also been noted elsewhere.<sup>15</sup>

Meads and his associates<sup>10</sup> presented a study of the effect of penicillin treatment in scarlet fever in children. They likewise studied the effect of this drug on the carrier state, noting a depression of the number of organisms obtained from the nose and throat, as demonstrated culturally. A reduction of the number of hemolytic streptococci was also observed under sulfonamide therapy, as had also been described by Julianelle and Seigel.<sup>7</sup> These authors also studied the effect of penicillin spray on streptococci in the nose and throat and were unable to obtain a significant decrease in the organisms present.

Hamburger and his associates<sup>4,5</sup> recently studied the carrier problem and came to the conclusion that a certain percentage of persons are "dangerous," in that they carry streptococci in their noses for months. Positive nasal cultures were found to be a more significant index of the carrier state than throat cultures. These findings are essentially in accord with those of DeLamater

\* Work done under the Army Air Forces Rheumatic Fever Control Program, Keesler Field, Mississippi, while the authors were in the Army of the United States.

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and others<sup>2</sup> who found persistent positive cultures to be associated with definite nasopharyngeal pathologic changes. Numerous carriers and cross infections due to carriers who had persistent nasopharyngeal disease were noted.

The present paper will deal further with the carrier problem and the effect of penicillin on the carrier state.

SOURCE OF MATERIAL

DeLamater and his co-workers reported the occurrence and development of an epidemic of streptococcal disease in an army camp during the winter of 1944 and 1945. This epidemic was produced by a single strain of group A, type 17 (Lancefield) hemolytic streptococcus<sup>16</sup> which was specifically resistant to the sulfonamides. The epidemic developed in the face of sulfadiazine prophylaxis. Cases derived from this epidemic afforded an opportunity for a large scale study of the therapeutic effect of sulfadiazine and penicillin, as well as an opportunity for an evaluation of their effects on the carrier state in the respiratory diseases caused by hemolytic streptococci. It may be pointed out further that this epidemic, because of its causation by a single specific type of streptococcus, offered a unique opportunity to observe and study not only the range of variation of the disease produced by a single strain of a single type of streptococcus in a fairly uniform population, but also the effects of therapeutic agents in disease caused by such a single strain. Variations in the susceptibility of different strains and types of streptococci to a given therapeutic agent were automatically eliminated.

The epidemic occurred in young men of military age, and primarily in those new to military life. Table 1 demonstrates this. In 271 cases so analyzed in which type 17 streptococcus was the causative organism, 80 per cent had less than three months' service and

73 per cent were eighteen years of age. The population infected, therefore, was as uniform as could be expected.

TABLE I  
LENGTH OF SERVICE AND AGE OF PATIENTS

Length of service, months	Cases	Age, years	Cases
0-1	109	18	197
1-2	87	19	27
2-3	20	20	5
3-6	17	21-25	19
More than 6	38	26-30	14
		More than 30	9

Potential patients were all seen in sick call. All those who had sufficiently severe clinical manifestations of fever or rash, or a combination of these, were admitted directly to the hospital. As soon as possible, usually within six hours after admission to the hospital, throat cultures were obtained from all patients who had respiratory disease. During the latter part of the epidemic, isolation was strictly adhered to in all cases of respiratory disease. Patients who obviously had scarlet fever on admission were sent directly to wards set aside for them. Patients who had tonsillitis and nasopharyngitis were isolated as strictly as possible in the wards to which they were first assigned. Patients who had pneumonia were isolated.

*Methods.* All bacteriologic technics were the same as those described in a previous report.<sup>2,3,17</sup> Penicillin was made up by the usual methods for intramuscular injection.

Figure 1 demonstrates the pattern of the epidemic in total cases per week. This graph further shows the breakdown of the total cases into the four most common clinical conditions encountered. It is particularly interesting to note the distribution of the diseases. Scarlet fever was the most important single disease and reflects the epidemic pattern most closely. The differentiation of

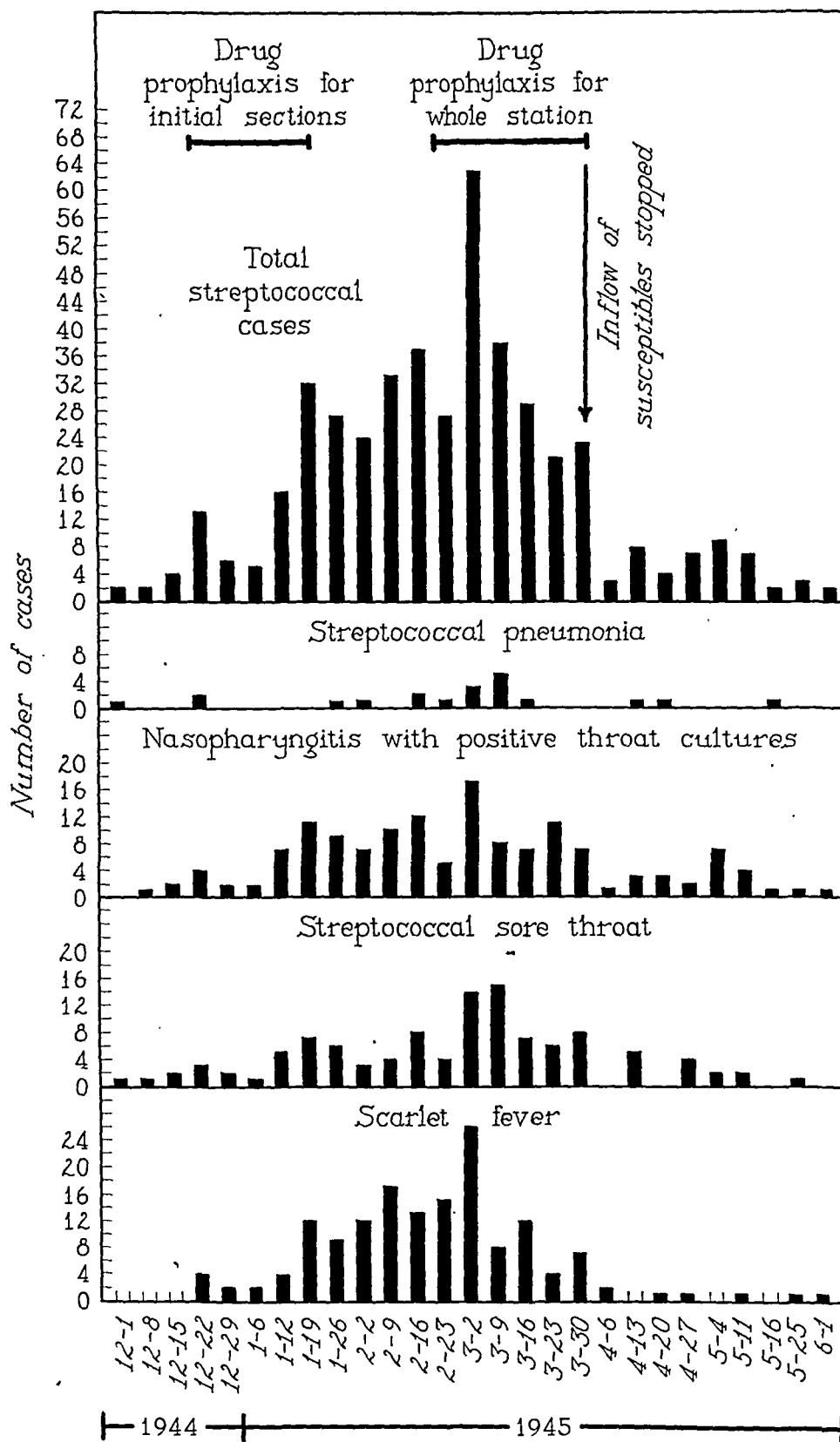


FIG. 1. Distribution of group A, type 17, streptococcal infections by weeks.



true streptococcal sore throat and nasopharyngitis with positive throat culture was made on clinical grounds. The patients who had nasopharyngitis without positive cultures differed in no way, either clinically or in the course of the disease, from those who had positive cultures, except that those who had positive cultures presented numerous problems of carrier control. We were never able to decide whether the positive cultures were incidental and clinically not significant, or whether this condition represented a very mild streptococcal disease which simulated a common cold (nasopharyngitis).

#### CLINICAL DESCRIPTION OF DISEASES ENCOUNTERED

*Nasopharyngitis with Positive Cultures.* This disease was mild. The men were acutely ill for twenty-four to forty-eight hours with temperatures ranging between 100° and 103°F. They suffered from acute malaise, headache, rhinitis and cough. The throat was injected but not follicular. After twenty-four hours of rest in bed and adequate intake of fluid, the fever and other symptoms subsided and the men were ready for full duty in three to five days. There were 111 such cases. They differed from the usual nasopharyngitis only in the occurrence of positive throat cultures for type 17 streptococcus.

*Streptococcal Sore Throat.* One hundred fourteen cases of streptococcal sore throat were observed. In these cases soreness of the throat developed with difficulty in swallowing. Temperatures of 102° to 104°F. (or higher) were present on admission and persisted for two to four days. The throat presented generalized erythema, with exudate on the tonsils or tonsillar pillars (or both) and follicles on the lymphoid tissue in the posterior pharynx. Treatment consisted of saline gargle, with the use of sulfadiazine in the early phase of the epidemic. Later penicillin was used in the more serious

conditions. Treatment of the complications followed that described under scarlet fever.

*Scarlet Fever.* During the winter of 1944 and 1945, 155 cases of scarlet fever due to group A, type 17, beta-hemolytic streptococci were studied.

Clinically the disease varied in intensity during this period. At the onset of the epidemic the disease was severe. It became milder toward the middle of the epidemic period but again became severe during the latter part. The rash was intense and appeared two to three days after the onset of sore throat. Sore throat was intense with marked dysphagia. The throats presented generalized, marked erythema, with exudate on the tonsils and tonsillar pillars. Edema of the pharynx was common. There was moderate toxicity with headache, weakness and vomiting with initial chills. In a tenth of the cases there was a hemorrhagic rash.

During the early stages of the epidemic, Schultz-Charlton tests done with commercial antisera gave negative results. In ten later cases the test was performed utilizing 0.2 cc. of convalescent serum from a patient who had recovered from type 17 scarlet fever. There was excellent blanching of the rash 2 cm. around the site of injection. Commercial scarlet fever antitoxin used in the same manner on the same patient gave negative results.

The patients in this series of scarlet fever were divided into three groups, according to the form of treatment which they received: those treated with penicillin, those treated with sulfadiazine and those treated symptomatically. These will be considered in detail later.

*Rheumatic Fever.* In only one case of group A, type 17 streptococcal infection did rheumatic fever develop. Approximately one week after the onset of severe hemorrhagic scarlet fever, aching and pain developed in all of the patient's joints. While

there was no swelling, redness or heat in any of the joints the patient was closely observed for rheumatic fever even though the early clinical picture was more that of infectious arthritis. The patient improved symptomatically when salicylates were administered, but repeated electrocardiograms and examinations of his heart failed to reveal any evidence of carditis. The sedimentation rate remained elevated for approximately seven weeks, and during the eighth week an aortic diastolic murmur was heard for the first time. Definite aortic insufficiency then rapidly developed and the diagnosis of rheumatic fever was apparent. The patient's antistreptolysin titer curve was typical of rheumatic fever.

In spite of the increased incidence of streptococcal infections there were fewer cases of rheumatic fever at Keesler Field during the winter and spring of 1944 and 1945 than had occurred in previous years. There seemed to be no relationship between the incidence of streptococcal infection (at least type 17) and the incidence of rheumatic fever. This is illustrated in Table II

TABLE II  
CASES OF SCARLET FEVER AND OF RHEUMATIC FEVER  
AT KEESLER FIELD

November-May	Scarlet Fever	Rheumatic Fever
1942-43	35	12
1943-44	19	10
1944-45	166	5

in which the total number of cases of scarlet fever associated with all types of streptococci is compared with the number of cases of rheumatic fever developing at Keesler Field during three years. This raises the question of whether the causation of rheumatic fever may be a specific character of a given strain or type of streptococcus. Keogh and Kelsey<sup>9</sup> expressed the belief that the disease pattern produced by a given strain of streptococcus

(as demonstrated in Figure 1) may be a rather specific character of the race, strain, or type under consideration.

*Streptococcal Pneumonia.* There were twenty cases in which group A, type 17, hemolytic streptococcal pneumonia developed. Seven of these were secondary to scarlet fever and were relatively milder than the primary streptococcal pneumonias caused by the same strain. Four of the patients had a massive pleural effusion and three others had pleurisy. All of these patients were treated with penicillin and made a satisfactory recovery except for one patient who is discussed under the heading "acute nephritis."

The cases of severe primary streptococcal pneumonia were characterized by a sudden onset with a temperature up to 105° and 106°F. The sputum was scanty, usually mucoid or mucopurulent, rarely blood-tinged and never frankly bloody. The leukocyte count was high, usually 20,000 or more per c.mm. of blood. With penicillin treatment the temperature fell over a three- or four-day period by lysis.

When an effusion developed it came early in the disease, so early in fact that in some instances it masked the underlying pneumonitis even on the first physical examination. The policy in these cases was to tap the thorax early and to instill penicillin into the pleural cavity. The fluid obtained was cloudy and amber colored and did not clot on standing. A direct smear failed to show the organisms, and, while they grew on culture, they did so only on blood agar plates in the presence of carbon dioxide. Several of these organisms had a distinctly greenish hue but were easily typed by the usual methods. In subsequent culture they lost their greenish coloration and grew readily aerobically. Instillation of 35,000 to 40,000 units of penicillin so sterilized the pleural fluid that positive cultures could not thereafter be obtained. These chests were

TABLE III  
COMPLICATIONS OF VARIOUS DISEASES

Diseases	Complications								Total Cases	Total Complications	Per Cent of Cases with Complications
	Cervical Adenitis	Otitis Media	Bacterial Pneumonia	Sinusitis	Pleurisy	Tonsillitis (recrudescence)	Peritonsillar Abscess	Other			
Scarlet fever . . . . .	43	19	7	12	3	2	3	13	155	102	65.8
Streptococcal sore throat . . . . .	12	8	2	6	0	0	9	7	114	44	38.6
Nasopharyngitis . . . . .	1	6	12	1	1	2	0	4	111	27	24.3
Streptococcal pneumonia . . . . .	2	2	0	2	3	0	0	1	20	10	50.0
Primary atypical pneumonia . . . . .	0	1	0	1	0	2	0	1	21	5	23.8
Miscellaneous streptococcal diseases . . . . .	2	0	0	0	0	0	0	2	18	4	22.2

tapped either daily or every other day with the instillation of penicillin after each tap. Three or four taps usually sufficed and in no case did empyema develop.

*Acute Nephritis.* A thirty-seven year old soldier who had two years' service entered the hospital for sore throat of two days' duration. Examination gave negative results except for a diffusely congested pharynx and purulent postnasal discharge consistent with nasopharyngitis and sinusitis. Throat culture on admission revealed group A, type 17, hemolytic streptococci. Urine on admission showed albumin 1+. The temperature on admission of 103.4°F. dropped to normal in five days under symptomatic treatment but there was thereafter a low grade fever with a temperature of 100°F. On the thirteenth day in the hospital the urine showed albumin 4+ and numerous erythrocytes and leukocytes. Blood pressure was 145 mm. of mercury systolic and 90 diastolic. Edema of the eyelids appeared. The urine continued to show albumin and cellular elements. The concentration of urea nitrogen rose from 16.6 to 66 mg. per 100 cc. of blood. Moist râles were

heard over the bases of both lungs and these, combined with tachycardia, falling blood pressure and temperature of 99°F. indicated myocardial failure. Anoxia developed and death occurred twenty days after admission.

Necropsy revealed subacute glomerulonephritis with interstitial bronchopneumonia of both bases due to group A, type 17, beta hemolytic streptococci. There was plugging of the bronchi, with atelectasis of the lower lobe of the right lung, and fibrous pleurisy of the lower lobe of the right lung. This was the only death which occurred at Keesler Field for which this organism was directly responsible. However, deaths occurred at other stations to which this strain of streptococcus was transmitted via troop shipments.<sup>12,14,17</sup>

#### COMPARISON OF COMPLICATION RATES IN THE DISEASES CAUSED BY GROUP A, TYPE 17, STREPTOCOCCI

A comparison of the complication rates of the diseases occurring in this epidemic is interesting. Table III shows the occurrence

of complications in the diseases observed. The percentage of complications gives an index of the relative severity of the three predominant diseases. As expected, more complications occurred in scarlet fever than in simple streptococcal sore throat, and relatively more complications in the latter disease than in nasopharyngitis with positive throat cultures. Streptococcal pneumonia lies halfway between scarlet fever and streptococcal sore throat in the incidence of complications. Interestingly, primary atypical pneumonia, which is of virus origin, parallels nasopharyngitis with positive cultures in incidence of complications.

Of all complications cervical adenitis was the most common, otitis media next and sinusitis third. Why there was such a high incidence of streptococcal pneumonia as a complication in the nasopharyngitis group was not apparent, but it seems likely that it was related to the difficulties encountered in the management of these patients, who considered themselves well by the second day of hospitalization.

#### THERAPEUTIC STUDIES IN SCARLET FEVER

The cases of scarlet fever were divided into three groups: (1) those in which treatment was symptomatic; (2) those in which sulfadiazine was used, and (3) those in which penicillin was used.

*Symptomatic Treatment.* A total of fifty-one patients who had group A, type 17, beta-hemolytic streptococcal scarlet fever were treated symptomatically. Basic treatment consisted of rest in bed for ten days, minimal fluid intake of 3,000 cc., zinc chloride astringent gargle for sore throat and acetylsalicylic acid for discomfort. In the initial cases in this group the disease was generally mild. Later cases were used as controls of the penicillin treated groups inasmuch as it was believed that penicillin could be used effectively for any complications that might arise. Despite the mildness

of the disease in the untreated group, the rash persisted for an average of six days as contrasted with four days in the group treated with penicillin. Fever persisted for five days in the untreated group in contrast to three days for the group treated with penicillin. The group treated with sulfadiazine fell midway between the two other groups, the rash lasting for five days and fever for four days.

The complications of the group that received symptomatic treatment are indicated in Table iv. They serve as a base line for the effectiveness of the other forms of treatment. Complications were treated with penicillin with excellent results. In cases of otitis media the tympanic membrane was incised at the onset. No permanent perforation or mastoiditis resulted.

Table iv shows a comparison of the complication rates of the three groups of cases. As expected, the symptomatically treated group had the highest percentage of complications (78 per cent). The higher percentage of complications which occurred in the group treated with sulfadiazine (70 per cent) as compared with the lower rate occurring in those treated with penicillin (55 per cent) is as expected. However, these results also suggest that sulfadiazine may have some effect in the body against an organism which is strongly resistant in the test tube and which otherwise clinically appears to be unaffected by the drug. The rate of complications in the sulfadiazine treated group lies between the other two. It should be emphasized that the group treated with penicillin includes all cases, no matter how or in what dosage the drug was given.

Table v shows nineteen of the cases in which symptomatic treatment was used, with a record of the throat cultures, indicated by the type of streptococcus isolated, taken daily or every three or four days. Unfortunately all cases in this group could not be

TABLE IV

COMPARISON OF COMPLICATION RATES IN THE THREE MODES OF TREATMENT USED

	Total Cases	Complication													Total Complications	Per cent Complications
		Cervical Adenitis	Otitis Media	Paranasal Sinusitis	Peritonsillar Abscess	Secondary Tonsillitis	Secondary Bacterial Pneumonia	Pleural Effusion	Erythema Multiforme	Rheumatic Fever	Nephritis	Septicemia	Sulfadiazine Reactions	Other		
Total cases of scarlet fever. .	155	43	19	12	3	2	7	3	1	1	0	0	4	7	102	65
Symptomatic treatment. . . . .	51	16	11	5	2	0	1	1	1	0	0	0	0	3	40	78
Sulfadiazine treatment. . . . .	30	8	2	2	1	0	1	1	0	0	0	0	4	2	21	70
Penicillin treatment. . . . .	74	19	6	5	0	2	6	1	0	1	0	0	0	1	41	55

followed culturally. The complication, day of complication and complicating type are also shown. The persistence of positive throat cultures for as long as thirty-five days is visualized. The carrier problem that this raises will be discussed more fully presently.

This group of nineteen cases in which cultures were taken does not reflect the total complication rate for the group. (Table iv.)

*Sulfadiazine Treatment.* There were thirty cases in which scarlet fever was treated with sulfadiazine. This group comprises the cases of scarlet fever that occurred between January 26, 1945, and February 15, 1945, before sulfadiazine prophylaxis was instituted for all personnel of the station. Generally this group represented milder cases than the initial group treated with penicillin. It was decided to treat this group of patients with sulfadiazine since penicillin was available only for cases of severe disease. These patients were treated with 4 Gm. of sulfadiazine daily for eight days. In general, the temperature dropped to normal in four to five days, with disappearance of the rash in five days. The throat continued symptomatically sore for three days in contrast

to the group treated with penicillin in which there was symptomatic improvement in twelve to twenty-four hours.

The complications in the group treated with sulfadiazine are shown in Table iv. The rates are significantly higher than in the group treated with penicillin when one considers that in these cases the disease was milder than in the cases in which penicillin was used. In cases of otitis media the tympanic membrane was incised and the patient was given penicillin for three to seven days. Complicating paranasal sinusitis was likewise treated with penicillin. One case of secondary pneumonia occurred which was also treated with penicillin.

It is noteworthy that the rate of occurrence of otitis media is much smaller in the group treated with sulfadiazine than in the group treated symptomatically. Although in the group treated with sulfadiazine the disease was generally milder, the difference may not be significant. However, it suggests at least partial inhibition of the growth of the organisms by the large doses used and suggests that there is a difference in drug sensitivity *in vivo*. However, daily throat cul-

tures of the patients treated with sulfadiazine showed persistence of the hemolytic streptococci in large numbers in the nasopharynx of these patients.

Table VI shows a group of seven of the patients treated with sulfadiazine who were followed by daily culture. The presence of the streptococcus is indicated by the type isolated. The complication, the day the com-

plication occurred and the complicating type, if definitely known, are also shown. The total dosage of the drug is also given. Here also the persistence of positive throat cultures is apparent. It is evident that sulfadiazine in the usual therapeutic dosage did not affect the carrier state.

The complication rate for the patients of Table VI was 42.8 per cent. The total com-

TABLE V

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED SYMPTOMATICALLY (NO SPECIFIC THERAPY)

Case	Day in Hospital																																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
1	..	17	...	...	17	...	...	...	17	...	...	0																								
2	..	17	...	...	17	...	...	...	17	...	0																									
3	17	17	...	...	17	...	...	...	17	...	17																									
4	...	...	...	17	...	...	...	17	...	...	0																									
5	17	...	...	...	...	...	...	...	...	...	17	...	...	17																						
6	..	17	...	...	...	17	...	...	17	...	...	...	17	...	...	0																				
7	..	17	...	...	...	17	...	...	17	...	...	...	17	...	...	0	...	...	...	17																
8	17	...	...	17	...	...	...	17	...	...	+	...	...	...	+	...	0	...	...	...	17															
9	17	...	...	17	...	...	0	...	...	...	17	...	...	17	...	...	0	...	17																	
10	17	..	17	...	...	17	...	...	...	17	...	...	17	...	...	17	...	...	0																	
11	...	...	...	17	...	17	...	...	...	17	...	...	17	...	...	19	...	...	17																	
12	..	17	...	...	...	...	17	...	...	17	...	...	...	17	...	...	0	...	...	...	17															
13	..	17	...	...	17	...	...	...	...	17	...	...	...	17	...	...	0	...	...	...	17															
14	..	17	...	...	17	17	17	17	17	17	0	G	17	17	17	17	17	17	17	NT	0															
15	..	17	..	17	17	NT	...	...	17	...	17	...	...	0	0	17	17	17	0	...	...	...	17	...	...	+	...	...	+							
16	..	17	...	...	...	...	...	17	...	...	C	...	...	17	...	17	...	...	...	17	...	...	17	...	17											
17	..	17	...	...	...	...	...	...	17	...	...	0	...	...	...	...	...	17	...	17	...	17	...	0	...	17	...	...	...	17	...	...	C	...	17	
18	..	+	17	...	...	...	17	...	...	+	...	...	...	17	...	...	17	...	...	...	17	...	17	17	17	17	17	17	C	17	17					
19	..	17	...	...	...	...	...	...	...	...	...	17	17	...	17	17	17	17	17	17	17	0	17	17	17	17	0	17	17	17	17	17	17	17	0	17

N.B.: NT = No type; C = Group C streptococci; G = Group G streptococci; + = Culture lost before grouping or typing was done.

TABLE V—(Continued)  
RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC  
STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED  
SYMPTOMATICALLY (NO SPECIFIC THERAPY)

Case	Complica- tion	Day of Complica- tion	Initial Type	Com- plicating Type
1	.....	.....	17	
2	.....	.....	17	
3	Cervical adenitis	3	17	17
4	.....	.....	17	
5	.....	.....	17	
6	.....	.....	17	
7	.....	.....	17	
8	Cervical adenitis	5 and 11	17	17 and 17?
9	.....	.....	17	
10	.....	.....	17	
11	Cervical adenitis	4	17	17
12	Cervical adenitis	7	17	17
13	.....	.....	17	
14	.....	.....	17	
15	.....	.....	17	
16	Cervical adenitis	5	17	17
17	.....	.....	17	
18	Cervical adenitis	5	17	17
19	.....	.....	17	

plication rate for the patients treated with sulfadiazine was 70 per cent. (Table iv.)

*Penicillin Treatment.* The group treated with penicillin totaled seventy-four patients. Penicillin was used initially in the cases of more severe illness since it was early known that the offending strain of streptococcus

was resistant to sulfadiazine. Later in the season, in order to avoid overtreatment of individuals sensitive to sulfadiazine, penicillin was given to the patients who had received sulfadiazine prophylactically.

Initially, the patients in the penicillin group were treated with 25,000 units intramuscularly every three hours. Treatment was continued for twenty-four hours after the temperature fell to normal. The dosage averaged 425,000 units in three days. The initial results were dramatic. The soreness and swelling of the throat subsided in twelve to twenty-four hours, so that the patient could comfortably swallow solid food at the end of the first day. Evidences of toxicity subsided in this period. The rash continued to spread to the extremities but was less intense. The rash on the trunk began to fade in twenty-four hours with total disappearance in three to four days, in contrast to six to seven days in the cases in which treatment was symptomatic. This suggested that toxin formation in the pharynx had diminished or ceased owing to penicillin treatment and that the spread of the rash was due to the dissemination of the toxin already liberated. However, as the season progressed and the number of complications increased, despite the initial favorable response to the drug, it was decided that administration of penicillin was being discontinued too soon, without complete destruction of the offending organism. This was in keeping with the experience of Plummer. Later, alternate patients were treated for seven to ten days, the total dosage ranging from 1,000,000 to 1,760,000 units of penicillin, with gratifying results as shown in Table vii.

Daily throat cultures were taken on patients receiving penicillin. It was observed that the initial cultures, those positive for beta-hemolytic streptococci, became negative after one day of penicillin therapy and remained negative during the period of treatment. However, a large proportion of

TABLE VI

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED WITH SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS

Case	Day in Hospital																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
20	17	0	17	17	17	17	0	..	17	..	17	17	..	..	..	..	..	17								
21	..	17	17	..	0	17	17	0	17	17	0	17	17	17	17	..	..	17	..	..	..	..	..	..	19	
22	17	17	17	17	17	17	17	0	0	17	17	17	0	..	17	17	17	17	..	..	17					
23	..	..	17	0	17	17	17	0	0	17	17	17	17	17	..	..	NT	..	..	17	..	..	..	17		
24	..	17	17	17	17	17	0	19	17	17	0	0	17	NT	0	0	0	17	17	17	17	..	..	17		
25	..	17	17	17	17	17	17	17	17	+	17	17	17	8	17	17	17	17	17	..	..	..	17	..	..	0
26	..	17	..	..	0	..	17	0	0	0	17	17	17	17	17	..	..	17	..	..	17					

N.B.: NT = No type; + = Culture lost before grouping or typing was done.

TABLE VI—(Continued)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WITH SCARLET FEVER TREATED WITH SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS

Case	Total Sulfadiazine, Gm.	Complication	Day of Complication	Initial Type	Complicating Type
20	36	Sulfadiazine reaction	9	17	
21	32	.....	..	17	
22	32	.....	..	17	
23	18	Sulfadiazine reaction	4	17	
24	32	.....	..	17	
25	34	Cervical adenitis	5	17	17
26	..	.....	..	17	

the cultures became positive one or two days or more after the cessation of treatment. This would indicate incomplete sterilization of the throat or reinfection, since the patients were kept in an open ward during the con-

valescent period. In a few patients who received large doses of penicillin after an initial ten-day period of symptomatic treatment, the throat cultures became permanently negative for hemolytic streptococci. This suggests that when some tissue immunity is built up against the streptococcus, the additional sterilizing effect

TABLE VII  
COMPLICATIONS AFFECTING ALTERNATE PATIENTS RECEIVING RESPECTIVELY SYMPTOMATIC TREATMENT AND PENICILLIN

	Symptomatic Treatment	Penicillin Treatment
Cases .....	15	15
Complications		
Secondary tonsillitis .....	0	2
Cervical adenitis .....	5	2
Suppurative otitis media ....	4	0
Paranasal sinusitis .....	1	0
Secondary pneumonia .....	1	0
Peritonsillar abscess .....	1	0



TABLE VIII  
RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCUS IN PATIENTS WITH SCARLET FEVER TREATED WITH (A) SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS; (B) PENICILLIN SUBCUTANEOUSLY, 100,000 UNITS ON THE TENTH, ELEVENTH AND TWELFTH DAYS AND (C) SULFADIAZINE, 1 GM. DAILY ON THE THIRTEENTH THROUGH THE TWENTY-EIGHTH DAY

Case	Day in Hospital*																																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28	29	33	34	35	37			
27		0	17	..	17	17	17	17	17	..	..	17	..	0	0	0	0	0	0	0	0														
28		..	..	17	0	..	17	17	17	..	17	17	17	0	NT	..	..	17	..	..	+	..	..	..	17										
29	17	17	17	17	0	0	17	17	17	0	17	0	0	0	17	..	..	..	..	..	17	..	..	..	17										
30	..	17	17	17	0	17	17	17	0	17	17	0	0	0	0	0	0	0	0	0	..	..	0	..	..	..	0								
31	..	17	17	17	17	17	0	17	17	0	0	0	0	0	17	0	0	..	..	0	..	..	0	..	..	..	..	..	..	0					
32	..	17	17	0	17	17	19	0	17	17	0	0	0	0	17	17	17	17	..	..	17	..	17	17	..	..	0	..	17	..	0				
33	NT	..	17	17	17	17	17	17	17	17	0	0	17	0	17	17	19	17	17	17	17	..	..	17											
34	..	B	17	17	17	17	17	17	17	17	0	0	..	0	0	0	17	0	17	17	17	17	..	..	..	..	17	..	17	0	..	..	17		

\* Days 27, 30, 31, 32 and 36 are omitted since no cultures were taken on these days.  
N.B.: NT = No type; B = Group B streptococci; + = Culture lost before grouping or typing was done.

TABLE VIII—(Continued)  
RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCUS IN PATIENTS WITH SCARLET FEVER TREATED WITH (A) SULFADIAZINE, 4 GM. DAILY FOR EIGHT DAYS; (B) PENICILLIN SUBCUTANEOUSLY, 100,000 UNITS ON THE TENTH, ELEVENTH AND TWELFTH DAYS AND (C) SULFADIAZINE, 1 GM. DAILY ON THE THIRTEENTH THROUGH THE TWENTY-EIGHTH DAY

Case	Total Sulfadiazine, Gm.	Total Penicillin, Units	Complications	Day of Complication	Initial Type	Complicating Type
27	48	960,000	Cervical adenitis	9	17	17
28	48	200,000	.....	..	17	
29	52	300,000	.....	..	17	
30	50	300,000	Cervical adenitis	20	17	?
31	44	300,000	.....	..	17	
32	39	300,000	Cervical adenitis	14	17	17
33	40	300,000	.....	..	17	
34	42	300,000	.....	..	17	

of penicillin is more potent than under other circumstances.

Table iv shows the complications encountered in the seventy-four cases in which penicillin was used. Cervical lymphadenitis appeared after administration of penicillin had been stopped on the fifth to fifteenth day, with local swelling of lymph nodes and rise of temperature. This condition subsided without suppuration under further use of penicillin. Suppurative otitis media occurred in 8.1 per cent of the cases from the fifth to fifteenth day of illness. The drum appeared red and bulging with hemorrhagic bleb formation. In all cases the drum was incised and the patients were treated with additional penicillin for three to seven days. Invariably, the drum healed uneventfully. Nasopharyngoscopic examination by Col. Percy Ross, M.C., revealed marked erythema and edema of the posterior nasopharynx with edema of the tissues

TABLE IX

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 200,000 UNITS PER DAY FOR THREE AND FOUR DAYS AS SHOWN BY BOXED AREAS

Case	Day in Hospital																																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
35	..	17	17	0	0	0	...	...	0	..	0	0	0	0	0	0	0	0	0																	
36	17	0	0	...	...	17	...	...	17	...	...	...	17	..	..	17	...	...	..	17																
37	..	17	...	...	17	...	...	...	...	...	...	17	...	...	+	...	...	...	17	...	...	+	...	...	0	+										
38	...	...	...	...	...	17	...	...	...	17	...	...	17	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	17	
39	17	...	...	...	...	...	...	0	...	17	...	...	...	17																						
40	..	C	..	17	17	0	...	...	0	...	17	...	...	..	17	...	...	17	+	...	+															
41	..	17	0	...	...	17	...	...	0	...	...	...	+																							
42	17	...	...	0	...	...	...	0	...	...	0	...	...	...	0																					
43	17	...	...	...	...	0	...	...	17	...	17	...	...	...	17																					
44	..	17	0	17	...	...	...	17	...	0	...	...	...	+																						
45	..	17	..	17	...	...	...	...	...	17	...	17																								
46	17	0	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	C																
47	..	17	17	0	0	17	17	17	17	17	17	17	17	17	C	B	17	17	17	NT	17	17														
48	17	17	..	0	0	0	0	0	0	0	17	17	17	17	17	17	B	17	0	17	17	17	17	17												
49	...	...	17	0	0	17	17	17	17	B	17	17	0	0	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	
50	17	B	0	17	17	17	17	17	17	17	17	0	17	17	17	0	0	0	17	0	B															
51	0	..	0	0	0	17	0	17	17	17	17	17	...	...	17	..	17	19	0	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	17	
52	..	0	17	0	0	...	17	...	17	...	17	17	17	17	0	17	17	0	...	...	0															
53	17	...	...	...	...	...	...	...	...	...	...	...	...	17	17	..	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	
54	..	17	..	17	17	..	17	17	17	17	17	17	0	17	17	17	17	0	17	17	17	17	17	17	17	...	...	...	B	17	0	17				
55	..	0	...	...	17	0	0	17	17	17	17	17	17	17	NT	17	0	..	17	17	17	17	...	...	...	...	...	...	...	...	...	...	19	..	17	
56	17	17	0	17	17	17	17	17	17	17	17	17	17	17	G	17	17	17	17	19	0	17	17	17	..	17	+	17	17	17	17					
57	..	0	...	...	0	0	17	17	0	17	19	17	17	17	17	17	0	17	17	C	17	0	0	0	17	17	17	17	17	17	17	17	17	17		
58	..	17	0	0	17	17	E	17	C	B	17	17	17	17	0	0	17	17	17	17	17	0	17	...	...	...	...	...	...	17	17					
59	..	0	0	0	G	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	0	17	0	17	0	0	17	17	0						
60	..	17	0	0	0	17	17	17	17	17	17	17	17	17	0	17	17	0	17	17	17	0	17	..	17	17	17	0	0	0	17					
61	..	17	0	0	0	17	17	17	17	0	17	17	0	17	17	17	0	0	17	0	..	0	0	17	0	0	...	...	...	...	...	...	17	..	17	
62	..	0	0	17	17	17	17	17	17	17	0	17	17	17	0	0	17	0	17	0	17	0	17	17	17	0	17	...	17							

N.B.: B = Group B; C = Group C; E = Group E; + = Culture lost before grouping or typing was done.

TABLE IX—(Continued)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 200,000 UNITS PER DAY FOR THREE AND FOUR DAYS AS SHOWN BY BOXED AREAS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
35	500,000	.....	..	17	
36	300,000	.....	..	17	
37	375,000	.....	..	17	
38	425,000	.....	..	17	
39	525,000	.....	..	17	
40	650,000	.....	..	17	
41	800,000	.....	..	17	
42	625,000	.....	..	17	
43	300,000	Cervical adenitis	8	17	17
44	300,000	.....	..	17	
45	425,000	Cervical adenitis	5	17	17
46	375,000	.....	..	17	
47	400,000	.....	..	17	
48	300,000	.....	..	17	
49	700,000	.....	..	17	
50	200,000	.....	..	17	
51	350,000	.....	..	17	
52	275,000	.....	..	17	
53	475,000	Otitis media	4	17	17
54	400,000	Cervical adenitis	13	17	17
55	300,000	.....	..	17	
56	675,000	Sinusitis	11	17	17
57	650,000	Sinusitis	11	17	19?
58	675,000	Cervical adenitis	11	17	17
59	500,000	Rheumatic fever	21	17	17
60	475,000	.....	..	17	
61	400,000	.....	..	17	
62	275,000	.....	..	17	

surrounding the eustachian tube. Paranasal sinusitis subsided under topical shrinkage of the nostrils and the use of penicillin. Secondary bronchopneumonia, which occurred in six cases, has been discussed under the heading "Streptococcal pneumonia." Rheumatic fever developed in one case in which the patient had received 500,000 units of penicillin during the first three days of scarlet fever. In this case the scarlet fever was severe as manifested by hemorrhagic rash. One soldier had a recurrence of malaria on the twenty-first day of his illness.

#### ANALYSIS OF PENICILLIN THERAPY

The description of the penicillin treatment series given in the preceding section applies to all cases in which penicillin was used, regardless of the amount received or the regimen of therapy of a particular patient. It is therefore not an entirely fair evaluation.

During the early phases of this study we were searching for the best methods of giving the drugs that were available for the treatment of scarlet fever and its complications. The series are not larger for two reasons. The first was the number of patients available for study; the second was the limitation in the supply of penicillin at the time of study. Data on eighty-seven patients treated with penicillin are analyzed in the following tables.

Each series of cases is presented with a table in which the period of treatment is indicated by boxed squares, the persistence of positive throat cultures is indicated by the type of streptococcus isolated and the total dosage of drugs is given in units or Grams. The complication, day of complication, and complicating type (if known) of streptococcus are also indicated.

Table VIII represents a series of eight patients who were first treated with 4 Gm. a day of sulfadiazine for eight days with the clinical response already noted. The effect on the throat cultures was negative. On the

tenth, eleventh and twelfth days these patients received 100,000 units of penicillin. All of these patients developed negative throat cultures while under this treatment. Two of the patients continued with negative cultures, six reverted to positive. It is interesting that the complications, in two of the three cases in which they occurred, developed late, on the fourteenth and twentieth days, respectively. Complications occurred in three cases, or 37.5 per cent. The ineffectiveness of this treatment in controlling carriers is evident.

Table ix lists twenty-eight patients who were treated intramuscularly with 200,000 units of penicillin per day for three and four days. In general, though not consistently, there was a temporary suppression of the positive throat cultures during the period of

treatment, which rapidly disappeared when administration of the drug was discontinued. In this series complications occurred in eight cases, or 28 per cent. In six cases the complications occurred on the eighth day of hospitalization or later. For the most part they were preceded by long persistent periods of positive throat cultures.

Ineffectuality of this treatment in controlling the carrier state is evident.

Table x lists eleven patients who received penicillin treatment during two separate periods. In the first period they received 200,000 units per day for two to four days; in the second period 100,000 units daily, on the tenth, eleventh and twelfth days of their disease. This was followed by 1 Gm. of sulfadiazine daily for thirteen to eighteen days. In this group the initial period of ad-

TABLE X

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WHO RECEIVED PENICILLIN 200,000 UNITS DAILY FOR TWO TO FOUR DAYS INITIALLY AND 100,000 UNITS DAILY ON THE TENTH, ELEVENTH AND TWELFTH DAYS FOLLOWED BY 1 GM. OF SULFADIAZINE DAILY FOR THIRTEEN TO EIGHTEEN DAYS

Case	Day in Hospital																																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35		
63	..	17	B	0	0	17	17	17	C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
64	..	17	..	0	17	17	17	17	..	..	0	..	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	
65	17	17	17	17	17	17	17	17	0	0	0	17	17	17	0	17	17	B	17	..	15	17	17	..	0	..	B	19	17	..	..	..	..	..	..	..	
66	17	17	17	17	19	17	17	17	17	0	17	17	0	0	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
67	..	17	0	17	17	17	17	17	17	0	0	0	17	17	17	17	17	17	17	NT	NT	0	0	17	17	17	17	17	17	..	..	17	17	..	..	..	
68	..	17	..	17	NT	0	0	0	0	B	B	0	0	0	5	0	17	17	17	17	17	17	17	17	17	17	0	0	0	..	17	17	..	..	..	17	
69	..	0	0	17	17	0	B	19	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	17	0	..	..	..	..	..	..	..	..	..	0	
70	..	17	..	17	0	17	17	17	17	19	0	17	0	0	0	17	17	17	0	0	17	..	17	17	17	17	17	17	17	17	17	17	17	17	17	17	
71	17	17	..	17	17	17	17	17	17	0	0	17	17	17	0	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	0	
72	..	..	0	0	0	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
73	19	..	19	19	19	19	17	19	0	17	0	19	0	17	19	19	17	19	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	0	

N.B.: NT = No type; B = Group B streptococci; C = Group C streptococci.

TABLE X—(Continued)  
RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI IN PATIENTS WHO RECEIVED PENICILLIN 200,000 UNITS DAILY FOR TWO TO FOUR DAYS INITIALLY AND 100,000 UNITS DAILY ON THE TENTH, ELEVENTH AND TWELFTH DAYS FOLLOWED BY 1 GM. OF SULFADIAZINE DAILY FOR THIRTEEN TO EIGHTEEN DAYS

Case	Total Penicillin, Units	Total Sulfadiazine Gm.	Complications	Day of Complication	Initial Type	Complicating Type
63	575,000	18	.....	..	17	
64	700,000	18	Sinusitis	9	17	17
65	600,000	13	Cervical adenitis	6	17	17
66	550,000	13	Cervical adenitis	8	17	17
67	650,000	16	.....	..	17	
68	1,000,000	18	Otitis media	3	17	17
69	625,000	18	.....	..	17	
70	700,000	18	.....	..	17	
71	575,000	18	Cervical adenitis	8	17	17
72	1,000,000	10	.....	..	19	
73	500,000	18	.....	..	19	

ministration of penicillin did not produce as marked a suppression of positive cultures as in the previous group. (Table ix.) The second period produced a temporary suppression in three cases. Spontaneous elimination of the organism apparently occurred in two cases. Complications occurred in five cases, or 66.7 per cent.

It is obvious in this group also that the dosage of penicillin did not control either the carrier state or the complication rate, which would appear to be associated with it.

Table xi demonstrates eight cases of scarlet fever due to group A, type 17, streptococcus in which 400,000 units of penicillin per day was given for three days. Thereafter the patients received 160,000 units per day for

three or more days, as indicated by the boxed areas. It now would appear that the dosage given is beginning to approach a useful range. Not only were the clinical benefits more striking than with the smaller dosages, but it will be seen that there was elimination of streptococci in five of the eight cases.

It would appear, however, that complications were not reduced, but in four cases the complications occurred before penicillin therapy was begun, in one case during the course of therapy and in one case after its completion. The total complication rate was 75 per cent, but in only 25 per cent (two cases) did the complication occur during or after treatment.

In Table xii sixteen cases are summarized in which 400,000 units of penicillin was given for three days and thereafter 200,000 units per day for two to seven days. The dosage here was the highest given and offers several interesting points. In all cases there was a suppression of streptococci during the course of treatment. In seven cases (43.8 per cent) there was practically complete suppression and elimination of streptococci with no development of further complications. In five of the remaining cases recurrence or persistence of streptococci in the nose and throat was associated with the development of complications. In two cases it might be argued that throat cultures again became positive because of the complications. In one case the reappearance of streptococci was not accompanied by complications.

It may be stated, then, that adequate dosage suppresses and eliminates a high percentage of streptococci from potential carriers, and that in carriers late complications are likely to develop.

In Table xiii a group of cases is described in which treatment was with penicillin spray. Although not all patients were followed for as long a period as might be

TABLE XI

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI ON PATIENTS RECEIVING PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS AND 160,000 UNITS PER DAY THEREAFTER AS SHOWN IN BOXED AREAS

Case	Day in Hospital																																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
74	17	...	...	...	17	...	...	0	...	...	...	0	...	...	...	...	...	...	...	0	...	0	0	0	17	C	..	B	..	..	17					
75	..	17	...	...	...	17	...	17	..	...	...	17	+	0	..	0	0	0	0	0	0	0	B	17	1	17	B	B	0	0						
76	17	17	...	...	...	17	...	+	...	...	...	17	0	0	0	0	0	0	17	17	17	C	17	17	17	C	17	17	17	17	17	17	17	17	17	
77	17	...	...	...	17	...	...	17	...	...	...	+	0	0	0	0	0	0	..	0	0	0	0	0	0											
78	..	17	...	...	17	...	...	+	...	...	...	+	0	0	0	0	0	0	0	0	0	0	0	0	0											
79	...	...	...	...	17	...	...	0	..	...	...	0	...	...	0	..	0	0	0	0	0	0	0	0	0	0	0	0	0	0						
80	..	17	...	...	17	...	...	17	...	...	17	..	0	..	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	..	0	0	0	0	0	
81	17	...	...	0	..	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	..	0	0	0	0	0			

N.B.: B = Group B streptococci; C = Group C streptococci; + = Culture lost before grouping or typing was done.

TABLE XI—(Continued)

RESULTS OF THROAT CULTURES FOR BETA-HEMOLYTIC STREPTOCOCCI ON PATIENTS RECEIVING PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS AND 160,000 UNITS PER DAY THEREAFTER AS SHOWN IN BOXED AREAS

Case	Total Penicillin, Units	Complications	Day of Complication	Initial Type	Complicating Type
74	1,000,000	Otitis media	5	17	17
75	1,480,000	.....	..	17	...
76	1,440,000	Sinusitis, Cervical adenitis	8 5	17 17	17 17
77	1,440,000	.....	..	17	...
78	1,440,000	.....	..	17	...
79	1,450,000	Otitis media	7	17	17
80	1,225,000	Otitis media	12	17	17
81	1,500,000	Otitis media	14	17	17?

desired, they demonstrate that penicillin spray to the nose and throat in the doses used was not sufficient to eliminate the streptococci. In no case did cultures become negative even during the course of treatment.

In two cases of scarlet fever caused by type 17 hemolytic streptococci and in one case caused by type 19 hemolytic streptococci, penicillin was administered by a continuous subcutaneous drip method. (Table xiv.) In one of the cases caused by type 17, and in the case caused by type 19 there was a temporary suppression of streptococci during the course of administration. In the third case a positive culture was obtained after a three day lapse and one day after administration of the drug was discontinued. In all three cases positive cultures were again obtained.

#### CROSS INFECTION AND THE CARRIER PROBLEM

The last four patients listed in Table xii are representative of one of the problems

encountered in this study. Such patients, even after long periods of freedom from positive cultures, again had streptococci in their throats and nasopharynges. Did they harbor the organisms during this interval, or did they become infected again during convalescence? It is believed that both conditions were operative. Those individuals who regularly carried the organisms consistently continued to have nasopharyngeal pathologic manifestations and undoubtedly belong to the “dangerous carrier” group of Hamburger. Others undoubtedly carried

the organisms in their ears, sinuses and elsewhere, and had hidden infections which were not reflected by culture.

That cross infections occurred is seen in many of the cases presented in the tables. Odd incidental types were isolated from throats from which a simple type only had previously been found. Cross infection with type 19 was most common. DeLamater and his associates have described the cross infection rate during the epidemic from which material for this report was derived.

Patients were also studied who had type

TABLE XII

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS, FOLLOWED BY 200,000 UNITS PER DAY FOR TWO TO SEVEN DAYS AS INDICATED BY BOXED AREAS

Case	Day in Hospital																																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
82	17	...	...	...	0	...	...	0	0	0	0	0	0	0	0	0																				
83	...	17	0	0	0	0	0	0	0	0	0	0	0	0	0	...	0	0	0	...	0	0	0	0												
84	...	17	...	0	17	0	0	0	0	0	0	0	0	0	...	0	0	0	0	0	0	0	0	0	0	...	...	0								
85	...	17	...	0	0	0	0	0	0	0	1	0	0	0	0	0	...	0	0	0	0	0	0	0	0											
86	17	...	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	0	0	0	0	0	0	0	0	0	0	...	...	0					
87	...	17	0	+	0	0	33	0	0	0	0	0	0	0	...	0	0	0	0	0	0	0	0	0	0	0	0	...	...	0	0	...	0			
88	17	0	...	...	...	0	...	...	0	...	...	...	0	0	0	0	...	...	...	0	0	0	0	...	0	0	0	0	0	0	0	0	0	0		
89	0	...	...	...	...	...	...	...	...	17	...	...	...	...	0	...	...	0	...	...	...	0	...	...	0	...	0	0	0	0	0	0	0	0	0	17
90	17	...	...	0	...	...	0	0	17	17	17	17	17	17	17	17	+	+	17																	
91	...	...	...	0	17	17	17	17	17	17	17	17	17	0	+	+	+																			
92	...	0	...	...	17	0	0	0	0	0	17	17	17	17	17	17	+	...	17	17	17	...	17	17	17	17										
93	...	...	...	0	...	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0	...	0	0					
94	17	17	0	...	0	0	0	0	0	0	0	0	0	0	0	0	0	...	0	0	0	0	0	0	0	0	0	0	0	17	17	B	B	17		
95	...	17	0	...	0	0	0	0	0	0	0	0	0	0	0	0	0	...	17	17	17	17	17	17	17	17	17	17	17	17	...	...	17	17		
96	...	17	...	17	...	0	0	0	B	0	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	...	17	17	17	17						
97	...	...	...	0	...	0	...	17	0	0	0	0	0	...	0	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	17	17	17	17	17	17

TABLE XII—(Continued)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH PENICILLIN, 400,000 UNITS PER DAY FOR THREE DAYS, FOLLOWED BY 200,000 UNITS PER DAY FOR TWO TO SEVEN DAYS AS INDICATED BY BOXED AREAS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
82	1,550,000	.....	..	17	
83	1,320,000	.....	..	17	
84	1,340,000	.....	..	17	
85	1,440,000	.....	..	17	
86	1,825,000	.....	..	17	
87	1,760,000	.....	..	17	
88	1,450,000	.....	..	17	
89	2,450,000	Pneumonia	3	?	17
90	1,650,000	Cervical adenitis	15	17	17
91	1,050,000	Cervical adenitis	7	17	17
92	1,140,000	.....	..	17	
93	780,000	Cervical adenitis	15	17	Not demonstrated
94	1,450,000	Mastoiditis	18	17	Not demonstrated
95	1,320,000	Tonsillitis	21	17	17
96	1,625,000	.....	..	17	
97	1,780,000	Tonsillitis	21	17	17

17 streptococci for as long as three months. Had sufficient penicillin been available, an effort would have been made to limit carriers by this means. It is apparent, however, from the foregoing that the amount of penicillin required for such an effort would have been prohibitive..

It would be desirable to have a study made of the effect of penicillin specifically on the so-called "dangerous carrier."

It appears to us that penicillin therapy offers a means for control of carriers pro-

vided adequate (large) doses are used over a sufficiently prolonged period.

# COMMENT

A study is presented of a series of cases of streptococcal disease, including scarlet fever, all of which were produced by a single strain of group A, type 17, hemolytic streptococcus. The evidence presented may corroborate Keogh in his belief that the relative proportion of the various diseases produced is a characteristic of a given strain.

Because this streptococcus was found to be resistant to sulfadiazine, and because there is evidence (as yet unpublished) to suggest that it became resistant during the early phase of this epidemic which it produced in the face of sulfadiazine prophylaxis, there was added incentive to study its response to other chemotherapeutic agents and antibiotics.

The implication is obvious that if these mutable organisms can become resistant to one antibacterial they may be capable of developing resistance against others. They therefore constitute a threat to existing means of therapy and control. The prophylactic use of drugs (such as sulfadiazine) necessitates the administration of relatively small doses (1 Gm. per day). The low drug levels so produced may be a stimulus to circumventing its action, and so actually aid in the production (or stimulation) of resistant mutants.

That penicillin may have a beneficial clinical effect in low dosage and still not eliminate these organisms completely from the nose and throat is apparent from the work presented. It is obvious that a maximal opportunity is thus given for the organism to produce resistant strains in the presence of the drug, if such is its proclivity.

It is also evident from the data that large doses are relatively more able to eliminate the streptococci and that with their elimination complications become less likely. Clinical



cally this fact alone warrants large initial dosage. It seems likely that even larger unit doses of the drug than those used here are justified, especially since the toxicity of penicillin is so low.

Because of the probability that the organism may be disseminated early to foci not easily eliminated by even large dosage, the earlier the drug is given the better. This can be justified on the basis of the occurrence of complications, as noted in the present study.

How such a program might affect the immunological picture is obscure and needs analysis. That some degree of immunity develops is implied by the relatively milder cases of pneumonia which occurred as complications secondary to scarlet fever.

The control of respiratory diseases remains one of the most common and difficult problems with which modern medicine must cope. The carrier is a menace, not only because of the droplets he exhales which directly or indirectly are sources of infection, but because of the contamination of the objects he touches. His control is an integral part of the problem as a whole.

It seems implicit in the data that the control of the usual and milder complications which apparently aid in the constitution of a carrier may prove to be one means of at least partial control of the basic problem.

SUMMARY AND CONCLUSIONS

1. The clinical disease produced in epidemic form by a sulfadiazine-resistant group

TABLE XIII

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER RECEIVING: (A) NO INITIAL TREATMENT, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (B) PATIENTS INITIALLY TREATED WITH 200,000 UNITS PER DAY FOR TWO TO FOUR DAYS, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (C) PATIENTS INITIALLY TREATED WITH SULFADIAZINE, 4 GM. PER DAY FOR SEVEN DAYS, LATER TREATED FROM TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY

Case	Day in Hospital																																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45				
98	17	.	..	17	...	...	0	...	...	...	17	...	...	17	...	...	...	0	...	17	..																												
99	..	17	...	17	17	17	...	...	17	...	17	...	...	0	0	17	17	17	0	...	...	...	17	...	...	...	+	...	...	+																			
100	..	17	...	17	17	0	0	17	...	...	17	...	...	17	0	17	17	17	17	17	17																												
101	..	17	...	0	17	17	17	17	...	...	0	...	...	0	17	17	17	17	17	17	17																												
102	0	...	0	0	0	17	0	17	17	17	17	17	...	...	17	...	17	19	0	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	17		
103	..	0	17	0	0	...	...	17	...	...	17	17	17	17	17	0	17	17	0	...	...	0																											
104	0	...	...	...	...	...	...	...	0	...	...	0	...	...	17	17	...	...	17	...	...	0	17	17	17	17	17	+	17	+	17	0	+	+															
105	..	17	...	17	...	...	...	0	...	...	G	0	0	...	17	0	0	0	0	0	17	NG	17	0	17	0	0	17	17	+	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17		
106	0	...	17	0	0	...	...	0	...	...	17	17	...	17	17	0	0	0	19	14	17	17	17	+	17	17	+	+	0	17	17	+	17	17	+	+	17	0	0	17	17	17	17	17	17	17	17		
107	..	0	...	...	...	...	...	...	...	...	...	...	...	0	17	17	17	17	...	...	17	...	17	17	17	0	17	E	0	17	17																		
108	17	..	17	17	0	17	17	17	17	17	...	...	17	...	0	17	17	0	17	17																													
109	..	0	17	17	17	17	17	...	...	17	...	17	CR	17	+	17	17	0	17	0																													
110	..	...	0	...	17	17	0	17	17	17	17	17	...	...	17	...	17	17	17	0	...	17	0	0	0	...	...	...	...	0																			

N.B.: CR = Cross reaction, positive hemolytic streptococci; NG = NO group, positive hemolytic streptococci; E = Group E streptococci; G = Group G streptococci; + = Culture lost before grouping or typing was done.

TABLE XIII—(Continued)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER RECEIVING: (A) NO INITIAL TREATMENT, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (B) PATIENTS INITIALLY TREATED WITH 200,000 UNITS PER DAY FOR TWO TO FOUR DAYS, LATER TREATED ON TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY; (C) PATIENTS INITIALLY TREATED WITH SULFADIAZINE, 4 GM. PER DAY FOR SEVEN DAYS, LATER TREATED FROM TENTH TO TWENTIETH DAY WITH PENICILLIN NOSE AND THROAT SPRAY, 1 CC. CONTAINING 10,000 UNITS, THREE TIMES A DAY

Case	Penicillin, Units		Sulfadiazine, Gm.	Complication	Day of Complication	Complicating Type
	Spray	Subcutaneous				
98	300,000	.....		..	.	
99	360,000	.....	..	.	.	
100	270,000	900,000	12	Sinusitis	2	17
101	300,000	400,000	1	Sinusitis	9	17
102	180,000	400,000	..	.....	..	
103	300,000	625,000	..	.....	..	
104	300,000	625,000	..	Cervical adenitis, Otitis media	9 2	17 17
105	300,000	1,500,000	..	Pneumonia	11	17
106	300,000	1,500,000	.	Otitis media, Pneumonia	22 14	17 17
107	300,000	.....	28	.....	..	
108	210,000	.....	28	.....	.	
109	270,000	.....	28	.....	..	
110	210,000	.....	28	.....	.	

A, type 17, hemolytic streptococcus is described. The origin of clinical material from a uniform population (age group) and its causation by a single strain of streptococcus afforded a unique opportunity for evaluation of the range of clinical manifestations produced by a single strain.

2. It is believed that this may be additional evidence for Keogh's hypothesis that the clinical range and proportion of disease produced by a given streptococcus are specific characters of that strain.

3. A comparison of the complication rates of the more important clinical diseases caused shows complete parallelism with the relative severity of each clinical entity, the rate being highest for scarlet fever, lowest for "nasopharyngitis" with positive culture.

4. Comparison of the complication rates of three forms of treatment used, that is, symptomatic, sulfadiazine and penicillin, is considered to be significant but the diverse management of the groups treated with penicillin prevents fair comparison.

5. Comparison of the clinical response to penicillin and sulfadiazine shows sulfadiazine to be ineffective, and penicillin, even in what is considered to be inadequate dosage for control of the infection, to be dramatic in its relief of symptoms.

TABLE XIV

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH CONSTANT SUBCUTANEOUS DRIP INJECTIONS OF PENICILLIN, 100,000 UNITS IN 1 LITER OF ISOTONIC SALINE SOLUTION DAILY FOR NINE TO ELEVEN DAYS

Case	Day in Hospital																																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
111	..	..	17	0	0	0	0	0	0	0	0	0	17	17	17	17	17	17	17	..	..	17	..	17	..	17	..	..	..	17					
112	..	17	..	0	17	17	17	0	0	0	17	0	0	0	..	0	0	0	0	17	17	17	..	..	17	..	..	17	17	+	..	17			
113	..	0	0	0	0	0	0	+	0	0	0	0	19	19	+	19	C	19	19	19	19	17	..	19	19	17	19	B	..	..	..	B	19	19	0

N. B.: B = Group B streptococci; + = Culture lost before grouping or typing was done; C = Group C streptococci.

TABLE XIV—(Continued)

RESULTS OF THROAT CULTURES IN PATIENTS WITH SCARLET FEVER TREATED WITH CONSTANT SUBCUTANEOUS DRIP INJECTIONS OF PENICILLIN 100,000 UNITS IN 1 LITER OF ISOTONIC SALINE SOLUTION DAILY FOR NINE TO ELEVEN DAYS

Case	Total Penicillin, Units	Complication	Day of Complication	Initial Type	Complicating Type
111	870,000	.....	..	17	
112	900,000	.....	..	17	
113	1,000,000	Tonsillitis	15	19?	19

6. Penicillin was found to be only partially effective in control of the carrier state, and then only in high dosage. The same may be said of the development of complications. It is believed that it is implied in the data, if not clearly demonstrated, that early and continued treatment with large dosage will offer some measure of protection against complications as well as against the carrier state.

7. There is strong evidence that in streptococcal disease complications and the carrier state are closely related.

8. When dealing with mutable or potentially mutable organisms, capable of becoming drug-resistant, early large dosage is indicated. Inadequate small dosage producing ineffective drug levels affords a maximal opportunity for mutable organisms to develop drug resistance.

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# Transfer of Beta Hemolytic Streptococci by Shaking Hands\*

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THE isolation technic employed in contagious disease hospitals recognizes the possible rôle of hands in the transfer of pathogenic micro-organisms by the strict attention paid to the washing of hands after contact with an infected patient. Our attention was drawn to this problem during a study of "dangerous" carriers of hemolytic streptococci during the war,<sup>1</sup> when it was found that large numbers of these bacteria could be recovered from the hands of nasal carriers, though those of throat carriers exhibiting negative nose cultures yielded very few or none at all. Further investigation revealed that gross contamination could occur instantaneously after blowing the nose. This was demonstrated by a simple test in which a carrier cleansed his hands, blew his nose into a sterile handkerchief, and then washed his hands in sterile broth, an aliquot of which was used for making a pour plate. It was not uncommon to recover hundreds of thousands of hemolytic streptococci by this test.

The hands of a nasal carrier emerged as a major *waystation* for hemolytic streptococci on their route from the carrier to a susceptible host. Their probable rôle in the contamination of secondary reservoirs in bedclothing and floor dust, and indirectly of the air, as well as in the pathogenesis of food-borne epidemics has been discussed in a previous communication.<sup>1</sup> Because of the ubiquity of handshaking as a social custom, it seemed advisable to determine how many

of these pathogens might be transferred when a nasal carrier shook hands with an uninfected person.

## MATERIAL AND METHODS

The carriers (referred to as "donors") employed in these tests were sailors undergoing primary training at the Great Lakes Naval Training Station, Illinois. They were detected by nose and throat surveys by Lieut. R. F. Platzer of Epidemiology Unit No. 13, and were sent to the University of Chicago for the experiments through the kindness of Captain L. D. Arbuckle, Senior Medical Officer at the Training Station. The uninfected subjects (referred to as "recipients") were normal persons whose nose and throat cultures were negative for hemolytic streptococci.

The procedure was as follows: (1) The recipient washed his hands for two to three minutes with soap and water, using a nail brush. He then soaked them in 70 per cent ethyl alcohol, washed off the alcohol with water and dried the hands with a clean towel. (2) He washed his hands in a basin of sterile broth for sixty seconds. (3) The donor shook hands with the recipient. (4) The donor washed his hands for sixty seconds in a basin containing 200 cc. sterile broth. (5) The recipient washed his hands in another basin containing 200 cc. sterile broth. (6) Aliquots of 0.1 cc. and 0.01 cc. from the donor's basin and 5 cc. from the recipient's basin were employed for making

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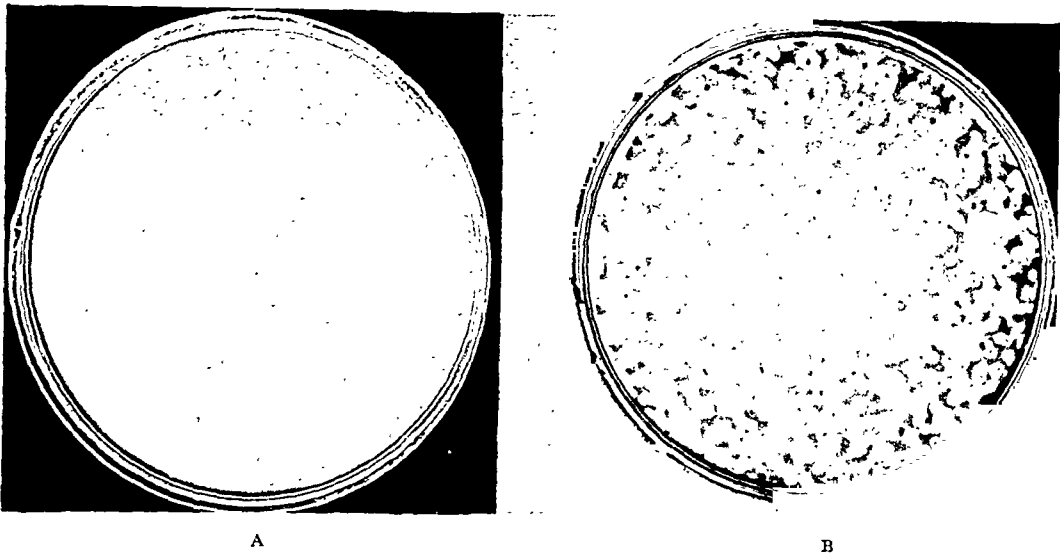


FIG. 1. Cultures of the hands of a non-carrier before, A, and immediately after, B, shaking hands with a nasal carrier of hemolytic streptococci.

blood agar pour plates. The plates were incubated twenty-four hours, following which colony counts for hemolytic streptococci were made.

The serological type of each carrier was determined by the bacteriological staff of Epidemiology Unit 13 by the method of Swift, Wilson and Lancefield.<sup>2</sup>

TABLE I  
HEMOLYTIC STREPTOCOCCI TRANSFERRED BY NASAL CARRIERS DURING HANDSHAKING—CARRIER BLEW NOSE IMMEDIATELY BEFORE SHAKING HANDS

Carrier No.	Streptococcal Type	Hemolytic Streptococci Recovered from Sterile Handkerchief into Which Carrier Blew Nose	Hemolytic Streptococci Recovered from Carrier's Hands	Hemolytic Streptococci Recovered from Recipient's Hands	
				Before Shaking Hands	After Shaking Hands
1	17	2,005,000	82,000	0	49,920
2	17	440,000,000	84,000	0	10,560
3	3	75,000	1,640,000	0	> 6,000
4	3	395,000	94,000	0	3,960
5	17	8,960,000	94,000	0	2,520
6	3	45,500	4,000	0	920
7	19	20,000,000	414,000	0	720
8	A	2,160,000	86,000	0	520
9	19	1,120,000	160,000	0	320
10	3	500	122,000	0	240
11	A	1,600,000	22,000	0	80
12	19	15,000	2,000	0	40
13	A	870,000	2,000	0	40
14	3	500	11,000	0	0
15	17	3,260,000	42,000	0	0
16	A	209,000,000	2,000	0	0
17	17	103,000	3,000	0	0
Average			169,000	0	4,450

RESULTS

Table I presents the results of seventeen tests in which the donor (carrier) blew his nose just before shaking hands with the recipient. The number transferred varied between none and 49,920, with an average of 4,450. Figure 1 is a photograph of the

TABLE II  
HEMOLYTIC STREPTOCOCCI TRANSFERRED BY NASAL CARRIERS DURING HANDSHAKING—DID NOT BLOW NOSE IMMEDIATELY BEFORE EXPERIMENT

Carrier No.	Streptococcal Type	Hemolytic Streptococci Recovered from Sterile Handkerchief into Which Carrier Blew Nose	Hemolytic Streptococci Recovered from Carrier's Hands	Hemolytic Streptococci Recovered from Recipient's Hands	
				Before Shaking Hands	After Shaking Hands
18	17	440,000,000	84,000	0	1960
19	Not A	3,160,000	86,000	0	1960
20	A	.....	10,000	..	600
21	A	870,000	2,000	0	480
22	A	1,600,000	22,000	0	40
23	17	2,005,000	82,000	0	40
24	17	8,960,000	94,000	0	0
25	A	200,000,000	2,000	0	0
26	17	103,000	2,000	0	0
Average			43,400	0	564

cultures of recipient No. 1 before and after shaking hands with carrier No. 1. The percentage of donors' streptococci transferred to recipients also varied considerably, but

averaged 2.6 per cent of the number recovered from the donors' hands.

In nine tests in which the donor had not blown his nose for one-half to three hours, fewer streptococci were transferred, the average being only 564 and the range 0 to 1960. These are presented in Table II.

It would appear then that the transfer of streptococci by shaking hands is more likely to occur when the nasal secretion on the hands is still moist.

Review of the tables reveals no direct quantitative correlation between the actual number of streptococci expelled from the nose and those recovered from the hands of any individual carrier, nor between the number on the hands of the donor and of the recipient. This is not surprising since factors such as the viscosity of the secretion, the mechanics of the act of blowing the nose, the dryness or moistness of the hands of both donor and recipient, and the technic and intensity of the handshake will strongly influence the number of streptococci finally transferred. It may or may not be a coincidence that the recipient whose hands were most heavily contaminated during the test was an extremely attractive young woman.

#### COMMENT

These results demonstrate that one of our oldest social customs, shaking hands, is not free of danger, though it is not our opinion that streptococcal infection is usually acquired by this means. Should a person who has just shaken hands with a nasal carrier put his own fingers into the mouth or nose or should he have a small open cut or other lesion on his own hands, he may, of course, become infected.

The possibility of transmitting both diphtheria and streptococcal infection by contaminated hands was recognized in 1919 by Weaver and Murchie,<sup>3</sup> who were able to recover diphtheria bacilli and hemolytic streptococci from the palmar surface of the right index finger and from beneath the nail

of internes and student nurses working in diphtheria wards. Positive cultures were occasionally obtained from door knobs on these wards. In 1926 and 1928, Hill and Matthews<sup>4</sup> and Matthews<sup>5</sup> published the results of experiments showing that hands swabbed with sputum or with cultures of tubercle bacilli, typhoid bacilli or diphtheria bacilli readily transferred the inoculated bacteria to a second person by shaking hands with him. In two of four experiments in which the first person shook hands with the second, the second with the third, and so on, *B. prodigiosus* swabbed on the hands of the first subject were recovered from those of the fifth.

#### SUMMARY

Quantitative cultures of the hands of nasal carriers of hemolytic streptococci and of individuals who shook hands with these carriers showed that several hundred to as many as 49,900 of these pathogens could be transferred by ordinary handshakes. The greatest numbers were transferred by carriers who had just blown their noses into sterile handkerchiefs.

We wish to express our thanks to Lieut. R. F. Platzer and the personnel of Epidemiology Unit No. 13 for their cooperation. Valuable technical assistance was rendered by Miss Carol Kraeger.

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# Clinical and Pathological Findings in Cases of Truncus Arteriosus in Infancy\*

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THE exact definition of a truncus arteriosus has been the subject of considerable discussion. For many years it was maintained that in order for the condition to represent a true truncus arteriosus there must be a single great vessel of abnormally large caliber, guarded by four semi-lunar valves, and the pulmonary arteries should arise directly from this vessel and the coronary arteries should arise from its base. During recent years the general consensus<sup>1,11,15</sup> has been that even though the orifice of the single great vessel may be guarded by two, three or four semi-lunar valves, the condition may still be considered as a truncus arteriosus, provided the coronary arteries arise at its base and the pulmonary arteries are given off from this great vessel.

Humphreys,<sup>11</sup> in her extensive study of this anomaly, presented evidence to show that cases in which the pulmonary arteries failed to meet the ventricles or the aorta, and in which the circulation to the lungs was by way of the bronchial arteries, represented an even earlier arrest in the formation of the great vessels than did a truncus arteriosus in which the pulmonary arteries arose directly from the aorta. She cited one case in which one pulmonary artery arose directly from the aorta and the other pulmonary artery ended blindly. The circulation to the latter lung was by way of the bronchial arteries.

A truncus arteriosus may, therefore, be

defined as a single great vessel of abnormally large caliber, from the base of which the coronary arteries arise, and which receives the blood from both ventricles and pumps the blood to the body and to the lungs by way of arterial pathways, i.e., either the pulmonary artery arises directly from the aorta or the circulation to the lungs is by way of the bronchial arteries. In most instances the ductus arteriosus fails to develop; it is never of functional importance.

Although a few cases have been reported in which the individual lived to late childhood<sup>17</sup> or early adult life,<sup>3,14,23</sup> the condition is usually fatal in infancy;<sup>2,5,13,15,22</sup> death frequently occurs within the first week of life. Except for Danelius's<sup>4</sup> report of the absence of the normal hilar "coma" found in cases of truncus arteriosus, virtually no attempt has been made to diagnose the condition during life. The following two cases indicate that in infancy a truncus arteriosus causes the heart to assume a distinctive contour; indeed the contour is so unique that the clinical diagnosis can be made with relative ease.

## CASE REPORTS

CASE I. W. T., (H. L. H. No. 99456), a colored male infant born July 5, 1936, was first seen at the Harriet Lane Home at three and one-half months of age because of heavy breathing, failure to gain weight and diarrhea. Physical examination revealed the temperature to be 37.2°C., pulse 150, respiration 50, weight 2.8

\* From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

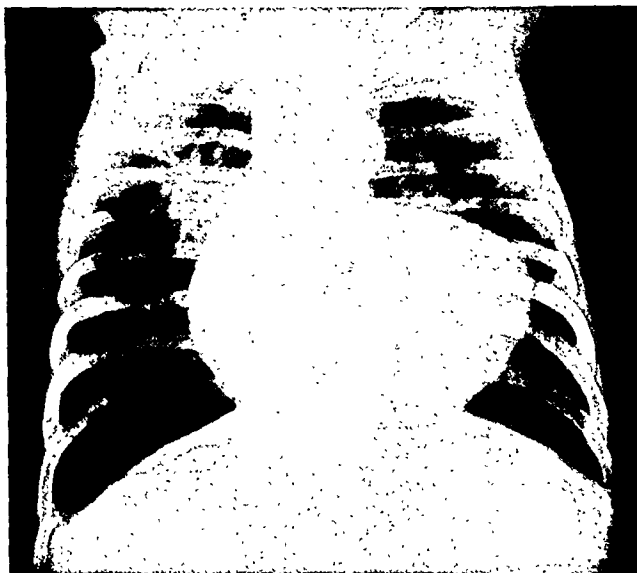


FIG. 1. X-ray of heart of Case 1 in anteroposterior view.

kilograms, height 56 cm. The general appearance was that of a markedly emaciated negro infant who was breathing rapidly and who showed slight but definite persistent cyanosis. The heart was enlarged. There was a harsh systolic murmur maximal over the heart which was well transmitted into the vessels of the neck and readily heard all over the posterior thoracic wall. The author thought the murmur was limited to systole; however, opinions on this point differed, and many persons thought there was a continuous murmur which extended throughout systole and diastole. The second sound at the base was accentuated and had the purity which occurs when there is but one great vessel. The lungs were clear. The liver extended halfway to the umbilicus but did not pulsate. There was a strong pulse in the femoral artery. The blood pressure in the arm was 80/50.

Laboratory data showed: red blood cell count 4.9 million per cu. mm., hemoglobin, 14 Gm. per 100 cc.

Fluoroscopic examination revealed a heart with a remarkable contour. In the anteroposterior view there was a sharp angulation of the cardiac shadow to the left of the sternum. There was no visible pulmonary conus; the aortic shadow was narrow but the aortic knob was conspicuous. (Fig. 1.) On rotation of the infant into the left anterior oblique position, the right ventricle appeared greatly enlarged and extended abruptly outward from the aorta to

the anterior chest wall. (Fig. 2.) The left ventricle also appeared to be huge.

Upon the administration of barium a sharp angulation of the esophagus was visible at the level of the prominent aortic knob. In addition, the lower part of the esophagus was displaced backward. In the anteroposterior view the displacement of the esophagus was even more striking. In the region of the left auricle it curved markedly to the left. (Fig. 2.)

The electrocardiogram showed relatively high P waves,  $T_2$  given off 2 mm. above the isoelectric line, and the wide ventricular deflection common in congenital malformation of the heart. There was no axis deviation. (Fig. 3.)

The clinical impression was that of a severe congenital malformation of the heart. The contour of the heart in the anteroposterior view distinctly showed a lack of the shadow cast by the normal pulmonary artery, a narrow aortic shadow and a pronounced aortic knob. The left auricle was huge and both ventricles were greatly enlarged. Although in the anteroposterior view the contour of the heart was similar to that of a non-functioning right ventricle, in the left anterior oblique position the contour indicated that the right ventricle was huge. In short, it was a new contour which suggested that there was a pulmonary atresia and that the aorta over-rode both ventricles and enlargement of the left auricle.

The patient failed to gain weight. He became



FIG. 2A.



FIG. 2B.



FIG. 2. X-ray of heart in Case 1 of left (A) and right (B) anterior oblique positions.

increasingly cyanotic and died of cardiac failure at four months of age.

*Autopsy Report No. 15057.* (Performed by Dr. Follis.) The heart was greatly enlarged. It measured 5 cm. in transverse diameter and lay more to the right than was normal. The superior vena cava and the inferior vena cava opened

normally into the right auricle, which was enlarged. The foramen ovale was completely sealed.

The right ventricle was a relatively small chamber but its wall was enormously hypertrophied; it measured 7 mm. in thickness. There was a defect in the membranous portion

of the ventricular septum. The large aorta arose above the defect. The aortic orifice was guarded by three semi-lunar cusps. The coronary arteries were normal. The pulmonary artery was a small, thin-walled vessel which branched to the lungs in the normal fashion, but ended blindly (Fig. 4) and did not communicate with the heart or the aorta. The ductus arteriosus was absent. No cord or remnant of the ductus arteriosus was found; moreover, there was no puckering in the aorta or the pulmonary artery to show where it had been. The left auricle was greatly enlarged. The left ventricle was larger than the right. It, too, was hypertrophied; its wall measured 9 mm. in thickness. An interventricular septal defect was clearly visible beneath the aorta. The aorta was enlarged; immediately above the aortic valve it measured 4.5 cm. in circumference. It became progressively narrower as it arched posteriorly.

The intercostal arteries were greatly dilated; their orifices were enlarged and the walls of these vessels were thicker than that of the pulmonary artery. The esophagus was found to be caught between the dilated intercostal arteries. (Fig. 4.)

One branch of a bronchial artery was injected and fluid emerged from the pulmonary artery and the pulmonary veins at the same time, which indicated that there was a definite anastomosis between the bronchial artery and the pulmonary artery. The anastomosis of the vessels was so extensive that the injection of the bronchial artery did not permit the differentiation of the bronchial arteries from the pulmonary artery.

*Anatomical Diagnosis:* Congenital malformation of the heart. Displacement of aorta, pulmonary atresia, high ventricular septal defect, premature obliteration of ductus arteriosus, closed foramen ovale, enlarged bronchial arteries, cardiac hypertrophy, chronic passive congestion and lobular pneumonia.

In brief, the malformation was that of a truncus arteriosus with the circulation to the lungs by way of the bronchial arteries.

*Comment.* The condition found at autopsy explained the clinical observation of the enlargement of both ventricles, the narrow aortic shadow and the large aorta.

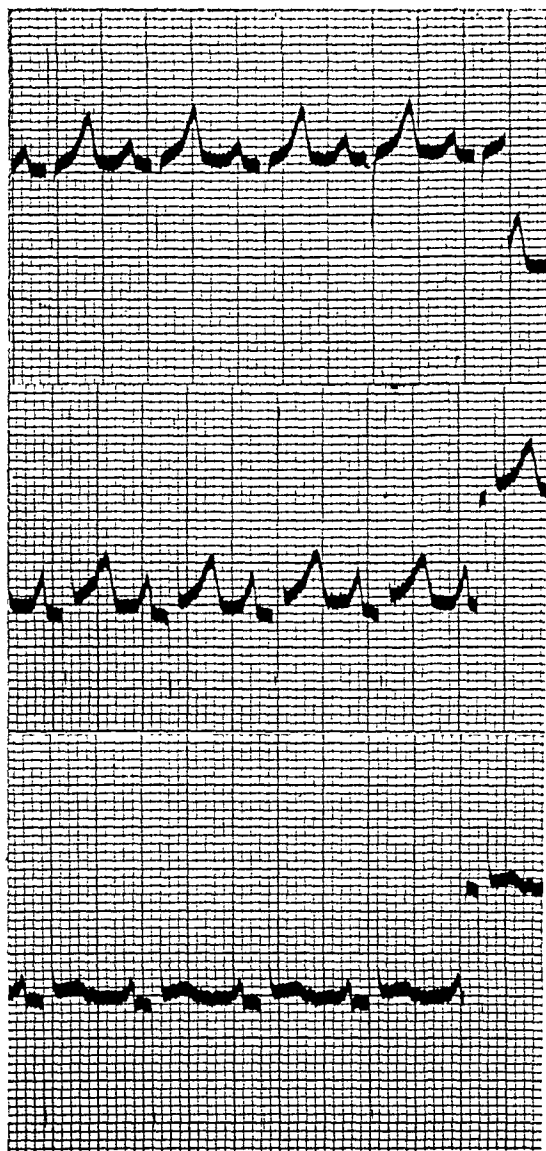
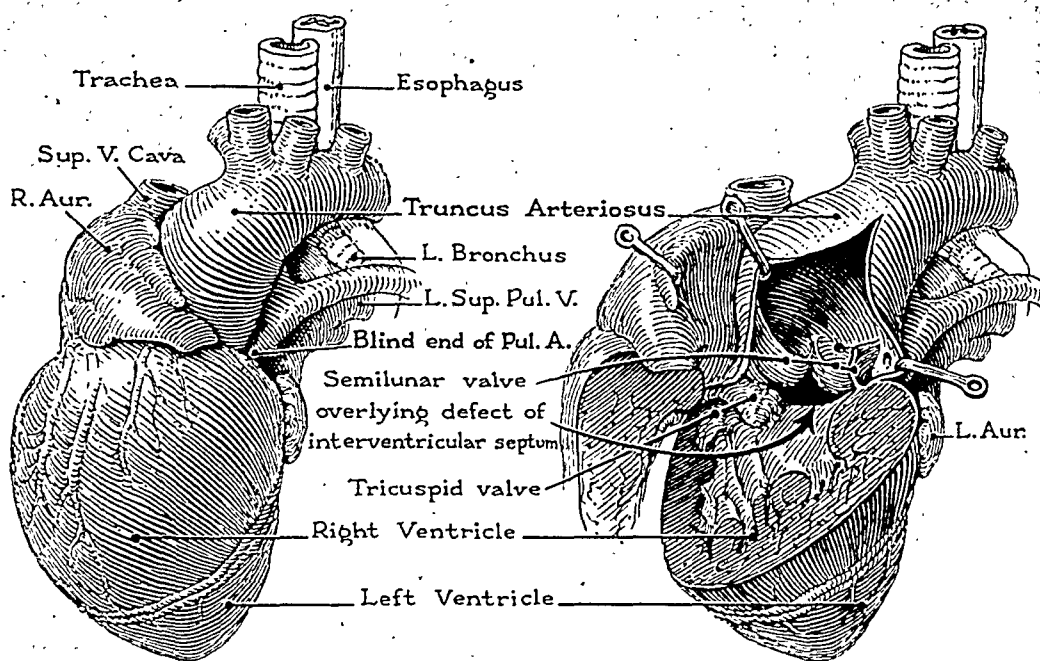


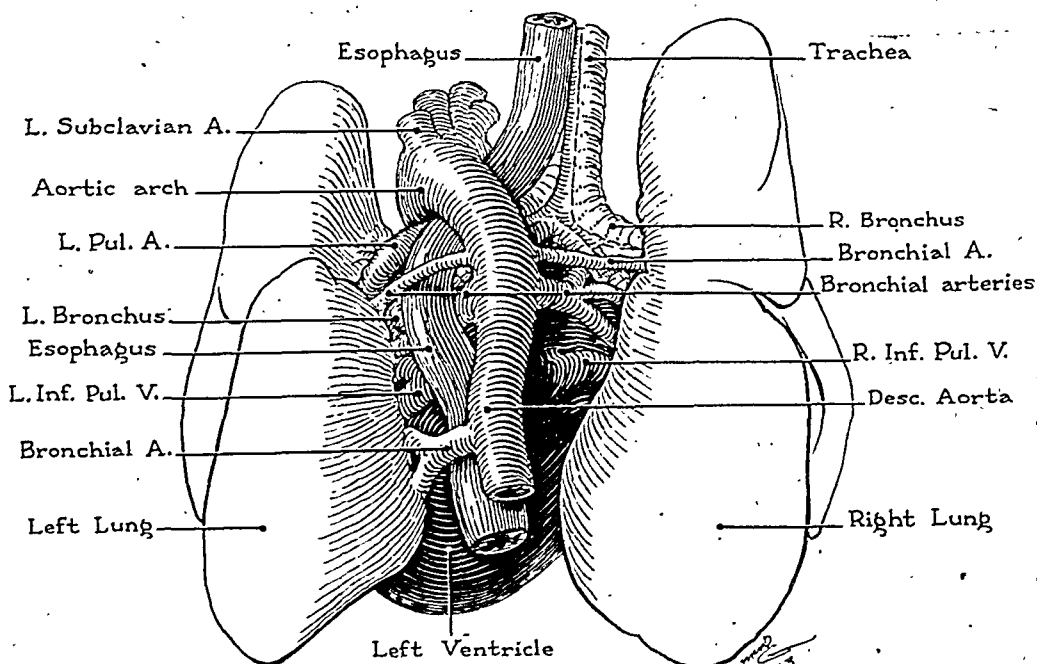
FIG. 3. Electrocardiogram of Case 1.

The distortion of the esophagus was in part due to the large left auricle (for which no adequate explanation was ever found) and in part due to the fact that the esophagus was caught between the dilated bronchial arteries.

**CASE II.** Baby H, a white female infant born February 6, 1943, at the Woman's Hospital was seen in consultation at ten days of age because of a heart murmur. The infant did well for the first week of life and then began to do poorly. Physical examination revealed the pulse to be 140, respirations 30 to 40 per minute. The infant's color was variable. At times it was



ANTERIOR VIEW



POSTERIOR VIEW

FIG. 4. Drawing of the heart of Case 1; a truncus arteriosus with the circulation to the lungs by way of the bronchial arteries.

normal and then it would become definitely cyanotic. Crying lessened the cyanosis. The heart was enlarged. The heart action was quiet; the sounds were of good quality. The second sound at the base was loud. There was a definite

precordial thrill and a harsh systolic murmur was heard all over the chest. The liver extended two fingerbreadths below the costal margin and did not pulsate. There was a strong pulse in the radial artery and in the dorsalis pedis.

Fluoroscopic examination showed the heart to be greatly enlarged. The right auricle was markedly dilated. The pulmonary conus did not appear to be full. In the left anterior oblique position the right ventricle was huge and extended abruptly out to the anterior chest wall. In the right anterior oblique position the esophagram was normal.

The clinical impression was that of a gross defect in the interauricular septum.

Three days later the infant became extremely dyspneic and the liver descended to the umbilicus. The following morning she died. The rapid failure of the circulation indicated a more serious malformation of the heart than an isolated gross defect in the interauricular septum. It was then realized that the abrupt angulation and the great enlargement of the right ventricle seen in the left anterior oblique position was consistent with a truncus arteriosus.

The final clinical diagnosis was: A gross defect in the interauricular septum and a truncus arteriosus with bronchial arteries. This diagnosis was made because of the similarity of the contour of the heart in the left anterior oblique position to that of the first case.

*Autopsy.* (Performed by Dr. Hellijas.) The heart was enormously enlarged. It extended to the left costal margin and almost filled the right hemithorax. The superior vena cava and the inferior vena cava opened into the right auricle in the normal fashion. There was an enormous defect in the interauricular septum; nearly half of the septal wall was lacking. The tricuspid valve had only two leaflets. The right ventricle was enlarged and its wall hypertrophied. At the base of the interventricular septum was a defect which communicated with the left ventricle. The pulmonary veins opened into the left auricle which was not enlarged. The mitral valve was normal. The interventricular septal defect lay beneath the base of the aorta. A single great vessel, the aorta or truncus arteriosus, arose above the defect in the interventricular septum and thus received blood from both ventricles. The orifice of this vessel was guarded by three semi-lunar valves, and the coronary arteries were given off in the normal manner. The pulmonary arteries were given off directly from the aorta. The ductus

arteriosus was absent and there was no indication in the pulmonary artery or in the aorta that it had ever existed.

*Final Anatomical Diagnosis:* Truncus arteriosus with the pulmonary arteries arising directly from the aorta, a gross defect in the interauricular septum and a high ventricular septal defect.

*Comment.* Autopsy confirmed the clinical diagnosis of a truncus arteriosus but showed that the pulmonary arteries arose directly from the aorta. The fact that the pulmonary artery arose directly from the aorta explained the occurrence of the transitory and minimal cyanosis.

#### COMMENTS

The first case is one of a truncus arteriosus with bronchial arteries. In the second case the pulmonary arteries arose directly from the aorta and even though the infant was but two weeks of age, no trace of a ductus arteriosus was found at autopsy. The two cases differed from each other in two important respects; first, in the structure of the interauricular septum, and second, in the pathway by which the blood reached the lungs. In Case 1, the circulation to the lungs was by way of the bronchial arteries; consequently, only a small volume of blood reached the lungs for aeration and only a small volume of oxygenated blood was returned to the left auricle and the left ventricle. This blood was mixed with the relatively large volume of blood which was directed to the systemic circulation and was returned by the superior vena cava and the inferior vena cava to the right auricle and the right ventricle. It follows that a small volume of oxygenated blood was mixed with a large volume of unoxygenated blood and only a small volume of oxygenated blood was pumped into the systemic circulation; cyanosis was intense. In the second case the pulmonary arteries arose directly from the aorta and the circulation to the lungs was far more adequate. Indeed, the circulation

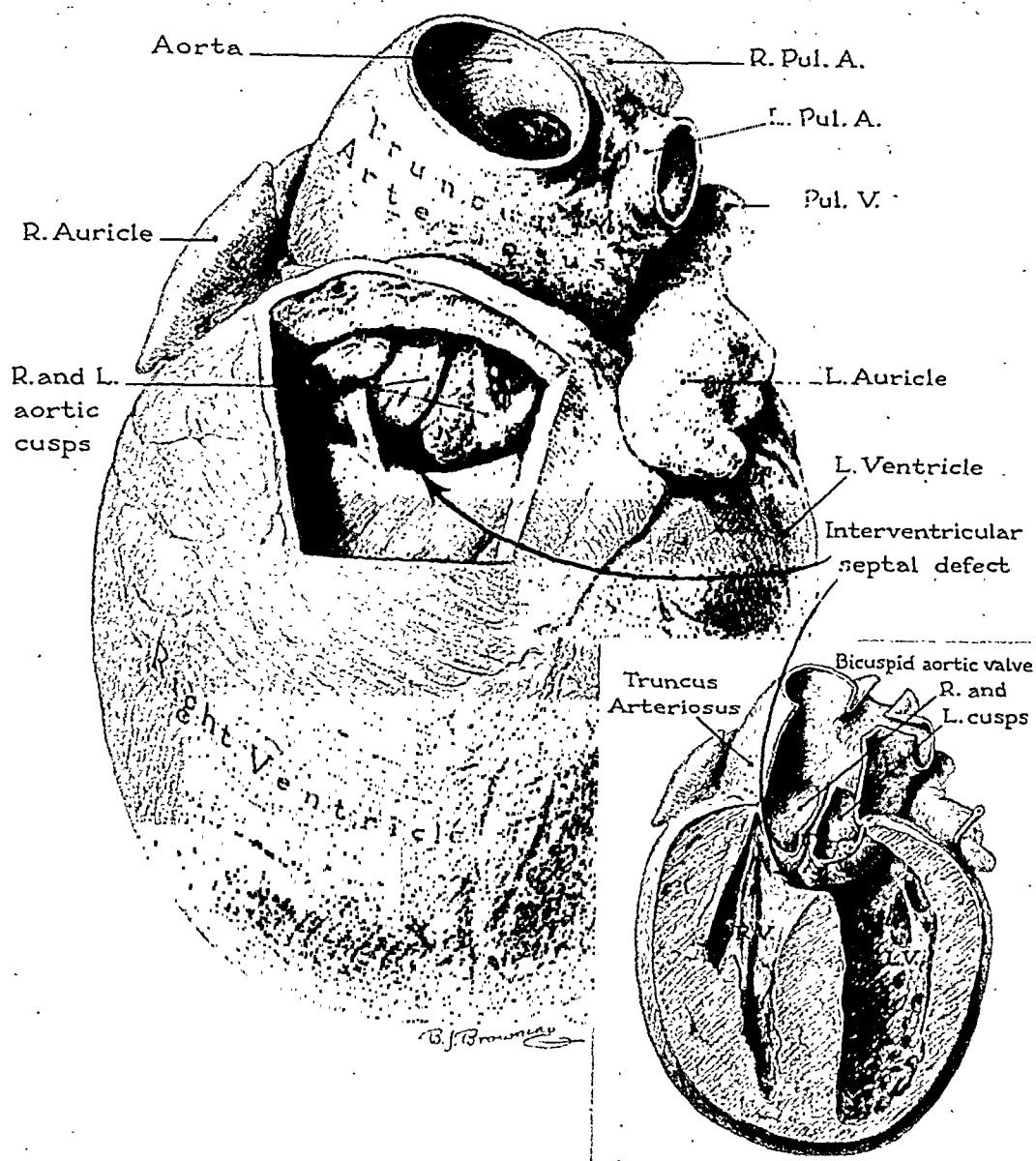


FIG. 5. Drawing of a heart, (illustrative of Case II); a truncus arteriosus in which the pulmonary arteries arise directly from the truncus arteriosus.

was such that when the oxygenated blood returned to the left side of the heart and was mixed with the venous blood returned from the body to the right side of the heart, there was no "visible" cyanosis.

These two cases differed greatly in the structure of the auricular septum. These differences were reflected in the fluoroscopic and x-ray findings. In the former, the left auricle was markedly enlarged, whereas in the latter, the right auricle was huge.

The structure of the ventricles was identical in the two cases. In both, the single great vessel arose directly from the two ventricles; consequently, in both instances there was a high ventricular septal defect. The structure of the heart in Case I is illustrated in Figure 4; a counterpart of Case II is shown in Figure 5, which, although drawn from a different specimen, is an exact replica, except that in Case II there was in addition a gross defect in the interauricular septum.

It is of interest and of significance that the contour of the ventricles in these two cases was identical. In Case II in the antero-posterior view the absence of the normal fullness of the pulmonary conus was not as striking as in Case I. Nevertheless, in the left anterior oblique position the right ventricle extended abruptly out from the aorta to the anterior chest wall as a shelf. To the best of my knowledge no other malformation causes such an abrupt shelf. Such a contour visualized in the left anterior oblique position is virtually diagnostic of a truncus arteriosus.

There are, in addition, two other features which aid in the establishment of the correct diagnosis. The first is the abnormally large aorta and the prominent aortic knob. A prominent aortic knob is rare in infancy. Indeed, normally the aortic knob is hidden behind the sternum. A large aorta should always arouse suspicion of the possibility of a truncus arteriosus. The second feature is one which Danelius<sup>4</sup> has emphasized, namely, the absence of the normal "coma" shadow. In my experience diminished hilar shadows are common in all malformations in which there is diminished blood flow to the lungs. It is seen in a truncus arteriosus with bronchial arteries but not when the pulmonary artery arises directly from the aorta.

The clinical feature which most sharply differentiates these two types of truncus arteriosus is the presence or absence of cyanosis. When the circulation to the lungs is through the bronchial arteries, cyanosis is intense; whereas, when the pulmonary arteries arise directly from the aorta, there is adequate circulation to the lungs and cyanosis is minimal or absent. Nevertheless, the contour of the heart in the two conditions is identical.

#### SUMMARY

Two cases of truncus arteriosus in infants are reported. In the first case the circulation

to the lungs was by way of the bronchial arteries and cyanosis was intense. In the second case the pulmonary arteries arose directly from the aorta; consequently, there was adequate circulation to the lungs and cyanosis was absent.

In both cases the contour of the heart in the left anterior oblique position was identical. In each instance the right ventricle extended out abruptly from the aorta to the anterior chest wall as a shelf. At autopsy the structures of the ventricles and their relation to the truncus arteriosus were found to be identical. Therefore, the author believes that this contour is characteristic of a truncus arteriosus in infancy in which the ventricles are normally formed and in which the aorta over-rides the ventricular septum and receives blood from both ventricles.

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# Influenza\*

## *A Preliminary State-wide Survey Using Routine Blood Specimens*

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THE quarter of a million blood specimens sent to this laboratory each year for serologic examination for syphilis should reflect the immunologic status of the residents of New York as regards various infectious diseases. They are reports from the field and may carry considerable information of value to health officers. Thus they might serve to reveal the prevalence and distribution of certain infectious diseases which are unreported or difficult to identify clinically. The suitability of the plan in the case of a particular disease would vary with the specificity and sensitivity of available technics and the ability to assemble samples which correctly represent the population being studied.

With these thoughts in mind, in the spring of 1945 we initiated the collection of pools of sera for a preliminary survey of the influenza antibody titer of persons living in New York State. Influenza seemed particularly suited to such an inquiry because of the established importance of laboratory diagnosis and the rather clear picture that has now been drawn of the significance of such information. Regarding the latter, it is only necessary to point out that the criterion of "excess pneumonia mortality"<sup>1</sup> does not distinguish between epidemics caused by influenza viruses A and B, while the apparent incidence of influenza is commonly distorted by the concurrence of other clinically indistinguishable upper respira-

tory infections.<sup>2</sup> The value of serologic tests has been demonstrated in many investigations. The rise of antibody levels after infection and epidemics and their slow fall thereafter<sup>3</sup> are well known, as is also the relative susceptibility of individuals with low-titered sera.<sup>4</sup> Serologic tests have served to identify the incitant of many outbreaks of the disease in recent years and to evaluate the results of vaccination<sup>5</sup> but they have not been methodically applied in a routine manner to so large an area as New York State (exclusive of New York City).

Finally, it should be noted that the fact that the periodicity of influenza may be explained by separating the cycles of influenza A and B and that these cycles may depend on the antibody status of the population<sup>6</sup> give added interest to a continuous state-wide survey.

The material so far examined includes three series of 300 to 350 pools, each of five sera. The first series was collected during the early summer of 1945; the second series, the following December, at the beginning of an epidemic of mild influenza; and the third series in the latter part of January and early February of 1946.

The pools consisted of specimens that did not react in the complement-fixation test for syphilis. For the most part, the more densely populated counties were represented by four urban and four rural pools, the less populous by four rural pools only. For this

\* From the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y.



TABLE I

TYPE-A AND TYPE-B INFLUENZA ANTIBODY TITERS OF ACUTE- AND CONVALESCENT-PHASE HUMAN SERA DETERMINED BY HEMAGGLUTINATION-INHIBITION AND BY COMPLEMENT FIXATION

Location of Cases	No. of Case	Age of Patient	Date of Onset	No. of Specimen	Date of Collection	Hemagglutination-inhibition Titer		Complement-fixation Titer	
						A(PR8)	B(Lec)	A(PR8)	B(Lec)
Kingston	1*	13	12/8/45	M7270	12/9/45	81	45	<2.0	<2.0
				R46-138	1/8/46	91	512	4.6	70
	2	13	12/8/45	M7269	12/9/45	203	64	5.7	<2.0
				R46-154	2/5/46	203	128	6.1	22
	3	35	12/12/45	R45-390	12/14/45	32	45	<2.0	<2.0
Ithaca				R46-135	1/7/46	111	456	4.5	74
	4	52	12/6/45	M7271	12/9/45	181	23	17	<2.0
				R46-136	1/8/46	294	194	13	36
	5	27	12/5/45	M7239	12/8/45	128	128	7.6	4.9
				R46-144	1/21/46	128	724	8.9	53
	6	21	12/5/45	M7240	12/8/45	223	256	7.4	13
				R46-143	1/21/46	256	813	6.5	47
	7	18	12/6/45	M7230	12/8/45	1290	256	9.8	6.7
				R46-139	1/21/46	724	645	4.3	>12
	8	18	12/4/45	M7242	12/8/45	362	64	7.9	<2.0
				R46-141	1/21/46	194	512	6.1	81
	9	21	12/4/45	M7244	12/8/45	304	91	8.1	<2.0
				R46-147	1/21/46	304	431	7.1	29
	10	19	12/4/45	M7232	12/8/45	256	6888	4.0	32
				R46-149	1/22/46	181	4096	4.5	30
	11	36	12/3/45	M7241	12/8/45	256	128	12	11
				R46-148	1/22/46	323	181	14	54
	12	17	12/3/45	M7228	12/8/45	362	181	6.3	<2.0
				R46-142	1/21/46	323	813	5.7	54
	13	20	12/3/45	M7234	12/8/45	128	91	12	11
				R46-152	1/22/46	152	1024	7.2	66
	14	19	12/2/45	M7229	12/8/45	208	181	9.0	<2.0
				R46-151	1/21/46	256	446	9.8	44
	15	21	12/2/45	M7245	12/8/45	161	128	12	<2.0
				R46-150	1/21/46	256	1024	7.5	33
	16	41	12/1/45	M7236	12/8/45	64	256	6.0	46
Albany County				R46-140	1/17/46	91	645	4.4	55
	17	17	11/30/45	M7231	12/8/45	512	1024	15	296
				R46-145	1/22/46	323	645	15	59
	18	13	12/10/45	M7317	12/11/45	114	23	10	<2.0
				R46-73	1/3/46	23	32	6.1	2.6
	19	12	12/10/45	M7314	12/11/45	114	45	5.0	2.2
				R46-71	1/3/46	45	84	2.9	1.5
	20	10	12/10/45	M7315	12/11/45	56	23	8.5	<2.0
				R46-67	1/3/46	74	23	3.6	<2.0
	21	8	12/9/45	M7316	12/11/45	128	45	9.2	<2.0
				R46-74	1/3/46	64	64	7.2	2.1
	22	8	12/8/45	M7313	12/11/45	102	23	<2.0	<2.0
				R46-69	1/3/46	47	23	3.8	1.7
	23	8	12/5/45	M7312	12/11/45	32	23	<2.0	<2.0
				R46-70	1/3/46	16	16	<2.0	<2.0
	24	9	12/4/45	M7311	12/11/45	215	45	7.2	4.0
				R46-72	1/3/46	105	114	5.6	7.5
	25	8	12/4/45	M7310	12/11/45	91	40	4.4	<2.0
				R46-68	1/3/46	49	23	3.4	<2.0

\* Influenza-B virus isolated.

study, centers with a population of 10,000 or over were classified as urban, those with less than 10,000 population as rural.

Serum specimens were also collected in December, 1945, during the acute and convalescent phases of infection from groups of patients in Kingston, Ithaca, and Albany County who had symptoms of acute upper respiratory disease tentatively diagnosed as influenza.

The sera were tested by Hirst's hemagglutination-inhibition technic<sup>7</sup> and the quantitative complement-fixation test developed in this laboratory,<sup>8</sup> which we have adapted to influenza.<sup>9</sup> The titers of the latter are expressed in terms of the maximum amount of complement required for 50 per cent hemolysis by a fixed quantity of serum (0.05 ml.) in the presence of antigen.

## RESULTS

*Sera from Patients.* The patients' sera yielded, in general, similar results with both technics. (Table I.) When compared with sera taken during the acute phase, none of the convalescent sera showed significantly increased titers for influenza-A virus by either method of testing. With the hemagglutination-inhibition technic, convalescent sera from all of the Kingston cases and seven of the thirteen Ithaca patients exhibited four-fold rises when tested with influenza-B virus, and three other Ithaca patients showed a two- to three-fold rise. In the complement-fixation test, the Kingston sera and ten of the Ithaca specimens showed marked increases in titer with influenza-B antigen; three of the Ithaca acute-phase sera had high titers and a rise was not demonstrated in the convalescent-phase specimens. The Albany sera, all of which came from children in one institution, did not show increased titers with either influenza-virus A or B by either method.

These results furnish data concerning the nature of the epidemic that occurred in New

York State during December, 1945. Evidently in the two areas in which influenza was diagnosed, the disease was due to influenza-virus B. Also, throat washings were examined for the presence of virus by amniotic inoculation of embryonated eggs and influenza-B virus recovered from one. This is of relatively little weight in determining the causative factor but is harmonious with the serologic evidence and general experience that the epidemic was predominantly due to influenza-B virus.

*Pooled Sera.* In contrast to the results obtained with the sera of patients, a considerable difference was obtained in the results when the pooled sera were tested by the two methods. Judged by the hemagglutination-inhibition method, there was little difference in the mean titers for influenza virus A and B for the three series. (Table II.) However, the proportion of pools in the second and third series with titers over 512 with influenza-virus A and B was lower than in the first series.

TABLE II  
INFLUENZA-A AND -B ANTIBODY TITERS IN POOLED HUMAN  
SERA DETERMINED BY THE HEMAGGLUTINATION-  
INHIBITION TECHNIC

Series	No. of Pools	Anti-gen	Maxi-mum Titer	Mean Titer	Per Cent with Titers of		
					<128	128-512	>512
I	349	A	912	336	12.0	71.4	16.6
II	348	A	1024	232	25.1	69.0	5.9
III	307	A	1024	290	7.5	85.9	6.6
I	349	B	840	274	28.2	55.1	16.6
II	348	B	1623	199	53.3	44.1	2.5
III	307	B	1448	209	32.1	65.3	2.6

The mean titers by the complement-fixation method were not markedly different in the three series. More strikingly the proportion of pools having high titers, that is above 10, with influenza-virus B antigen rose from 4.3 per cent to approxi-

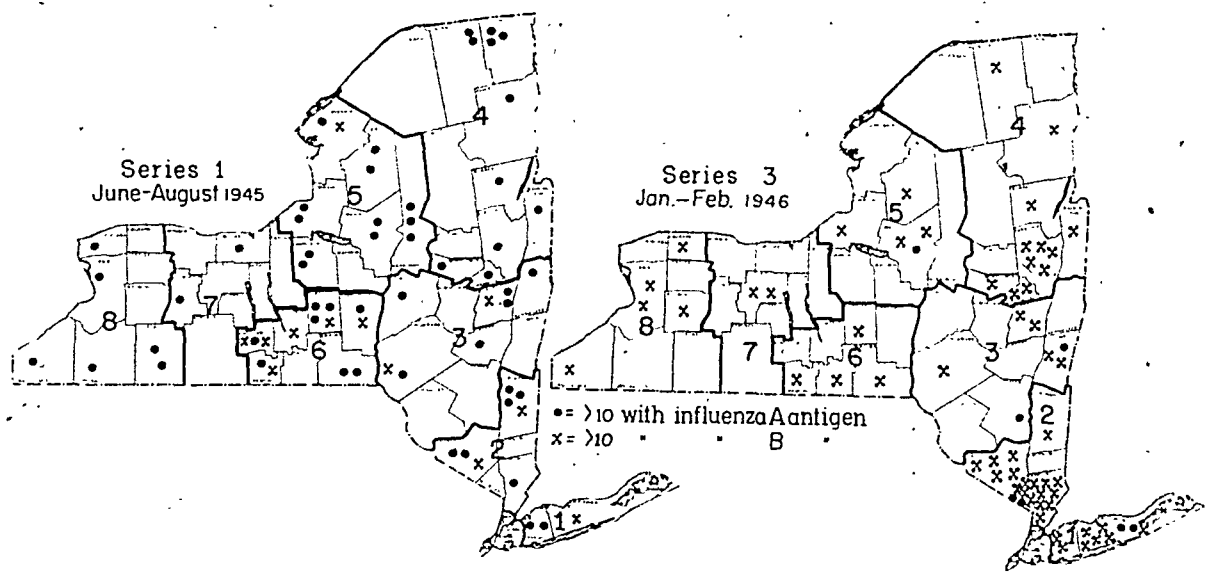


FIG. 1. Distribution of pools of sera with complement-fixation titers of over 10 with influence-A and -B antigens.

mately 18 per cent in the third series, whereas the proportion of pools with high titers for influenza-virus A fell from 16.3 to 2.3 per cent. (Table III.)

TABLE III  
COMPLEMENT-FIXATION TITERS OF POOLED HUMAN SERA  
COLLECTED IN 1945 AND 1946

Series*	Anti-gen	No. of Pools	Maxi-mum Titer	Mean Titer	Per Cent with Titers of		
					<5.0	5-10	>10
I	A	349	38	7.7	24.9	58.8	16.3
II	A	348	21	5.3	52.0	38.5	9.5
III	A	307	17	4.6	67.1	30.6	2.3
I	B	349	22	6.5	37.2	58.5	4.3
II	B	348	30	5.3	57.3	35.1	7.4
III	B	307	102	8.0	41.4	40.7	17.9

\* Series I collected June-August, 1945.  
Series II collected December, 1945.  
Series III collected January-February, 1946.

If the results of the complement-fixation tests are analyzed geographically (Fig. 1) it will be seen that the pools in the first series with high influenza-B titers were principally from medical region 6, whereas in the third

series, they tended to be grouped in those counties bordering New York City with smaller foci elsewhere. In the first series, pools with high influenza-A titers were scattered throughout the state; in series three, they were almost all in or close to regions 1 and 2.

COMMENT

While the usefulness of routine serum surveys of this kind can be established only through prolonged experience, the simplicity of the plan recommends it. The specimens required are constantly available without additional effort. Furthermore the pools can be held for further testing at a later date and may have as much future as present value. Collections of this kind have several times proven of considerable value to us. The size of the samples will doubtless need to be adapted to the problem at hand and it is probable that more precise selection of specimens according to a sound plan will become desirable in the case of influenza. What factors may be of greatest

importance in assembling the samples remain to be determined.

The differences in results obtained by the two methods of testing raise the question of their relative value for studies of this kind. Although the technic of the complement-fixation test used in these studies apparently indicated a sharper differentiation between acute- and convalescent-phase sera, there was close agreement between the two methods. The reasons for the divergencies noted in the results with the pooled sera are, no doubt, multiple. The dilution as a result of pooling and the relative sensitivity of the tests may be factors. The complex character of influenza antigens and antibodies must also be considered. Suffice it to say at this time that experimental evidence at hand makes it seem worth while to continue the study with the complement-fixation method.

#### CONCLUSIONS

The routine testing of serum pools may be of value as a public health laboratory procedure and may supply data useful in estimating the prevalence, distribution and susceptibility to certain diseases.

Pools from all parts of New York State exclusive of New York City have been periodically tested for influenza antibody titers.

The results suggest that influenza-A antibodies were relatively high in the summer of 1945 but steadily diminished thereafter. Influenza-B antibodies were relatively low in 1945 but increased in some areas following the epidemic of December, 1945.

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# Rheumatoid Arthritis\*

## *The Diagnostic Significance of Focal Cellular Accumulations in the Skeletal Muscles*

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THE diagnosis of typical, far advanced rheumatoid arthritis is not a difficult problem. However, the differentiation of this disease in its early and atypical forms from gout, osteoarthritis, infectious arthritis, rheumatic fever, and the "erythema group" first mentioned by Osler<sup>1</sup> is often a matter of conjecture. To confuse the differential diagnosis still further, there are such ill defined syndromes as fibrositis, palindromic rheumatism, Reiter's syndrome and what is sometimes referred to as "psychogenic rheumatism." Some of these patients, in particular those with fibrositis and palindromic rheumatism, may indeed be in the initial stages of rheumatoid arthritis.<sup>2</sup> The diagnosis of many of these conditions is based on the clinical picture and history alone, while in some there are laboratory procedures such as cultures, roentgenograms, agglutination studies and sedimentation rates to aid in the diagnosis. These, however, are often normal or equivocal.

The work of Freund<sup>3</sup> and his collaborators, therefore, is of particular interest. In 1945, they described the presence of clusters of lymphocytes, plasma cells and epithelioid cells among the muscle fibers of the amputated legs of a patient with rheumatoid arthritis. In addition to these accumulations of cells, they noted definite changes in the muscle cells, consisting of hydropic de-

generation, edema, loss of striation, marked swelling and atrophy of muscle fibers. They were able to demonstrate these same changes in muscle biopsies obtained in fourteen other cases of rheumatoid arthritis. In a control study, no such lesions were found, and the authors came to the conclusion that these pathological findings in rheumatoid arthritis were specific. The same results were reported in an additional paper by Steiner, Freund, Leichentritt and Maun.<sup>4</sup> It was concluded here that the cellular accumulations in the endomysium occurred in the early stage of the disease and preceded the degenerative changes in the muscle fibers. Similar cellular infiltrations of the perineural and periadventitial perimysium were also found in later stages of the disease.

During the past year an effort has been made to confirm the findings of Freund and his collaborators, and further to ascertain whether muscle biopsy could aid when the diagnosis was obscure. Dawson<sup>5</sup> believed that there was little justification for separating rheumatoid arthritis in which "atrophic" changes predominated from "non-specific infectious" arthritis. He pointed out that a similar course, similar roentgenograms, agglutinins for hemolytic streptococci and subcutaneous nodules occur in both. In this study these groups have been separated for the sake of analysis.

\* From the Department of Internal Medicine, the Department of Pathology, and the Department of Surgery, Yale University School of Medicine. Aided by a grant from the Fluid Research Fund of the Yale University School of Medicine.

## MATERIAL

The patients studied were from the Arthritis Clinic, the Orthopedic Clinic and the Medical and Pediatric wards of the New Haven Hospital. Biopsies were taken arbitrarily from the bellies of the deltoid and the gastrocnemius muscles. With the aid of  $\frac{1}{2}$  per cent novocaine, blocks of muscle tissue 1 cm. in greatest diameter were removed.

In all, biopsies were performed on thirty-one patients. Sixteen of the thirty-one biopsies were from clinically typical rheumatoid arthritis of the "atrophic" type. Eight of the sixteen were males and eight were females. The duration of disease in the group was two to eighteen years. With the exception of two, all were in the active phase of the disease as judged by clinical pictures and sedimentation rates. There was roentgenographic evidence of osteoporosis and narrowing of the joint spaces in each case, and nine of the sixteen patients had been given gold therapy prior to the time the biopsy was done.

The other fifteen were included in the study either as controls or because the diagnosis was obscure. Among the nine controls there were two cases of rheumatic fever, and one case each of osteoarthritis, hypochondriasis and gonococcal arthritis, and four cases of "non-specific infectious" arthritis. Further controls were obtained from twenty-three autopsies in whom no rheumatoid arthritis was present. These autopsy controls were selected only on the basis of being within the same age range as our cases of rheumatoid arthritis. The group included three patients with generalized arteriosclerosis, two with tuberculosis, three with rheumatic fever, one traumatic death, two suicides and one each with carcinoma of the lung, carcinoma of the lip, Hodgkin's disease, liver abscess, glomerulonephritis, fatty liver, subacute bacterial endocarditis, dissecting aneurysm, diabetes mellitus, duo-

denal ulcer, Guillain-Barré's syndrome and cerebellar glioma.

## RESULTS

All of the pathological findings both of the rheumatoid arthritis cases and the controls are included in Table I.

The biopsies of thirteen of the sixteen cases with rheumatoid arthritis showed focal

TABLE I  
INCIDENCE OF LESIONS IN PATIENTS WITH ARTHRITIS OF  
VARIOUS TYPES AND ALSO IN AUTOPSY CONTROL  
GROUP

	No. of Patients	Cellular Foci		Muscle Fiber Changes*
		Peri-vascular in perimysium	Endomysial	
Rheumatoid Arthritis	5 5 3 2 1 — Total 16	+ + — + —	+ — — — +	+ — — + +
"Non-specific Infectious" Arthritis	1 1 1 1 — Total 4	+ — — —	+ + — —	— + + —
Osteoarthritis	2 1 1 — Total 4	— + —	— + —	— + +
Gonococcal Arthritis	1 — Total 1	—	—	—
Rheumatic Fever	4 1 — Total 5	— —	— —	— +
Autopsy Cases	11 6 — Total 17	— —	— —	— +

\* Including increased eosinophilic staining, loss of definition of myofibrils and striations, vacuolization, atrophy and proliferation of fibroblasts in endomysium.

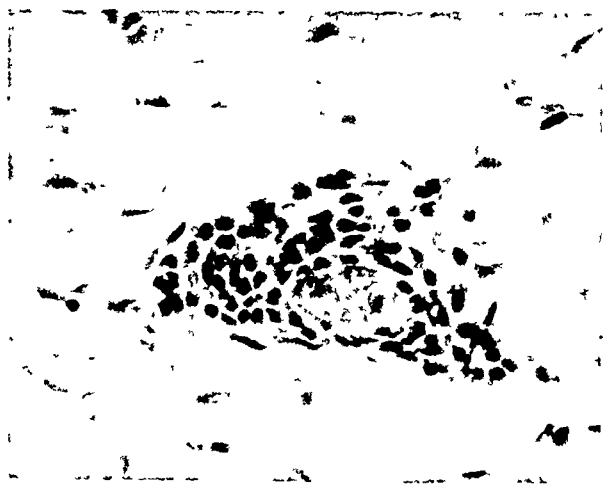


FIG. 1. Perivascular focal cellular accumulation. Case No. 26; hematoxylin eosin. 580 X.

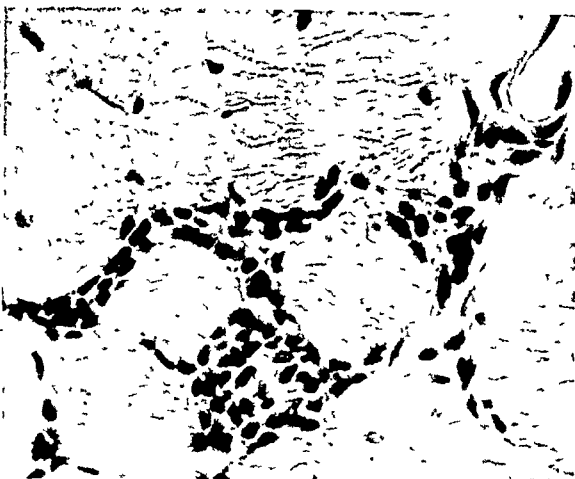


FIG. 2. Cellular accumulations in endomysium surrounding uninvolved muscle fibers. Case No. 26; hematoxylin eosin. 580 X.



FIG. 3. A focal accumulation of cells in perimysium adjacent to an arteriole. Case 19; hematoxylin eosin. 270 X.

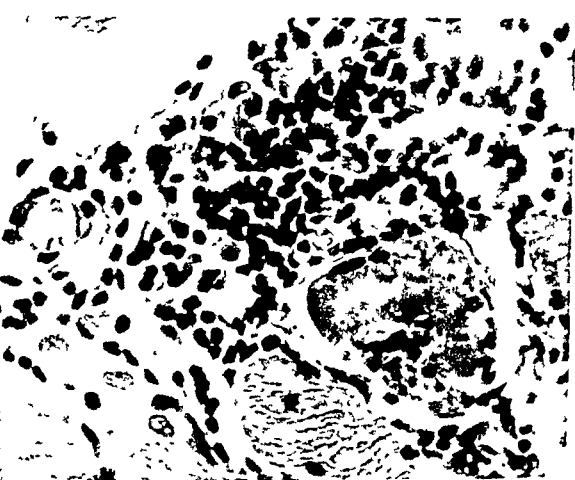


FIG. 4. Focal cellular accumulation in perimysium in proximity to hyaline degenerating muscle fiber. Case 13; hematoxylin eosin. 580 X.

cellular accumulations. These consisted of collections of lymphocytes, with fewer macrophages and rarely scattered plasma cells and eosinophiles; they were most commonly located perivascularly in the perimysium and less frequently in the endomysium between the individual muscle fibers. The perimysial foci were not related to the small nerve branches nor were changes noted in the walls of the small arteries or veins lying in juxtaposition to the foci. (Figs. 1, 2 and 3.) Changes found in the muscle fibers were interpreted as degenerative. These included increased eosinophilic staining, loss of defini-

tion of the myofibrils and striations, vacuolization and atrophy. Fibroblasts were increased in number but there was no conspicuous fibrosis. (Fig. 4.) These muscle changes were in most instances, though not always, accompanied by cellular foci in the endomysium; the latter were also at times unassociated with muscle fiber degeneration. Necrotic foci, conspicuous accumulation of polymorphonuclear leukocytes and bacteria could not be found.

There seemed to be no correlation between the presence of a positive biopsy and the duration of the illness. The lesions found

in patients with old, inactive disease did not differ in character or extent from those found in active cases, nor did there seem to be any relation between the presence of these muscle changes and gold therapy. The presence of a positive biopsy could not be correlated with the degree of atrophy of the muscle biopsied.

With the exception of one patient who may have had lupus erythematosus disseminatus, there were no clinical features to distinguish the three cases of rheumatoid arthritis with negative biopsies from those with positive biopsies. Two of the three had Marie-Strümpell arthritis as well as disease of their peripheral joints.

It was of interest to find that two of four patients with "non-specific infectious" arthritis showed the same cellular foci as those found in the cases of rheumatoid arthritis.

Muscle was studied from one patient with clinical osteoarthritis and from three autopsies in which the diagnosis of osteoarthritis had been made as an incidental finding in routine x-rays. The biopsy from the clinical case showed changes indistinguishable from those in the rheumatoid arthritis group. This patient gave a history of having had twenty years previously, a three-month febrile illness associated with polyarthritis. The sections from the autopsied cases showed no cellular foci, but in one of the three there were hyalin degenerated muscle fibers.

Muscle from five patients with acute rheumatic fever has been studied. Two were clinical cases and three were taken from the autopsy material. No cellular foci as observed in the rheumatoid group were found. Hyalinization and vacuolization of the fibers, however, were present in one. No lesions were found in the muscles of the remaining seventeen autopsy controls.

The six cases included in the study who were diagnostic problems were of particular interest. The differential diagnosis in each

case rested between rheumatoid and some other form of arthritis. In only one was the biopsy positive. This patient subsequently developed fairly typical rheumatoid arthritis although her x-rays are still negative. The remaining five patients, whose biopsies were negative, continue to be diagnostic problems.

#### COMMENT

Not all cases of rheumatoid arthritis have yielded positive biopsies, yet in these studies the cellular foci in the muscles were found only in cases that were clinically classified as rheumatoid arthritis and "non-specific infectious" arthritis, with the exception of one patient with clinical osteoarthritis who gave a history suggestive of old rheumatoid arthritis. These findings would give no indication of any fundamental difference between the "atrophic" and "non-specific infectious" forms of rheumatoid arthritis.

How early in the course of the disease these inflammatory foci appear is not known, but that they can appear before x-ray evidence of joint disease is manifest is shown by the one case in the group presenting a diagnostic problem in which a positive biopsy was obtained before x-ray changes were present in the joints. The nature of the focal lesions is unknown. Pathologically, they consist of collections of cells of the type seen in chronic inflammatory foci, most commonly in perivascular locations, but also in the endomysium between the individual muscle fibers. Lesions of the adjacent vessels were not found nor were the foci related to the nerve fibers. There was no necrosis found in association with the perimysial foci. No other stage of the process was detectable; the appearance was always essentially the same. Fibrosis was insignificant.

Changes in the muscle fibers, at times definitely degenerative in type, were fairly frequent. Such fibers were often but not



always surrounded by cellular accumulations. The pathogenesis of hyalinization and loss of definition of myofibrils and their striations is not known. This alteration was also found in some of the control series. It may be related to their terminal illness but certainly is not peculiar to rheumatoid or "non-specific infectious" arthritis.

The presence of these skeletal muscle changes along with subcutaneous nodules and the findings of endocardial and myocardial lesions reported by Baggenstoss and Rosenberg<sup>6</sup> and by Bayles<sup>7</sup> is further evidence that rheumatoid arthritis is a systemic disease. The fact that such lesions were not found in our rheumatic fever controls is of interest in relation to the discussion concerning the relationship of rheumatoid arthritis and rheumatic fever.

#### SUMMARY

Muscle biopsies were obtained in sixteen cases of rheumatoid arthritis in an effort to repeat the work of Freund<sup>3</sup> and his collaborators. As controls, biopsies were obtained in fifteen other patients among whom were included cases of osteoarthritis, rheumatic fever, gonococcal arthritis, and "non-specific infectious" arthritis; similar studies were made in twenty-three routine autopsy cases.

Muscle lesions were found in thirteen of the sixteen cases of rheumatoid arthritis and in two of the four control cases of "non-specific infectious" arthritis. With the exception of one patient with osteoarthritis who had a history suggestive of rheumatoid arthritis these lesions were absent from all

other controls. Our results would give no indication of any fundamental difference between the "atrophic" and the "non-specific infectious" forms of rheumatoid arthritis.

The lesions consisted of focal accumulations of lymphocytes and macrophages and occasional plasma cells and eosinophils occurring either in perivascular locations in the perimysium or in the endomysium between the individual muscle fibers. Hyalinization, vacuolization, loss of striations and atrophy of muscle fibers were found frequently in association with these cellular foci in the above group, while in the controls similar degenerative changes occurred without any cellular reaction.

These cellular accumulations would appear to be further evidence of the systemic nature of rheumatoid arthritis. Although they have not been found in all cases of this disease, their presence has been limited almost exclusively to rheumatoid arthritis. Their nature is unknown, and their direct relationship to the duration or activity of the disease is as yet undetermined.

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## The Diagnosis of Guillain-Barré's Disease

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WITHIN recent years there has appeared an increasing interest in the symptom complex known as Guillain-Barré's disease. Actually, this illness has been recognized since 1892 when Osler<sup>1</sup> first described it under the term of "acute febrile polyneuritis." However, since that time it apparently has been lost in the maze of specialized literature and has been revived periodically under different titles (radiculoneuritis—Guillain, Barré, and Strohl;<sup>2</sup> acute ascending paralysis—Casamajor;<sup>3</sup> acute infective polyneuritis—Bradford, Balford, and Wilson;<sup>4</sup> infective neuritis—Kennedy;<sup>5</sup> polyneuritis with facial diplegia—Francois, Zuccole, and Montus<sup>6</sup> and Taylor and McDonald;<sup>7</sup> myeloradiculoneuritis—Shaskan, Teitlebaum, and Stevenson;<sup>8</sup> encephalo-myelo-radiculitis—Polan and Baker,<sup>9</sup> etc. Currently this illness has become widely accepted as Guillain-Barré's disease since these investigators first emphasized one of the most characterizing features of the illness, namely, a low spinal fluid cell count associated with an elevated protein. Actually these investigators reported twelve cases, all of whom developed a flaccid paralysis of the limbs with some involvement of both deep and superficial sensation. All their cases showed an increased spinal fluid protein of 1 to 2 Gm. and all recovered without residuals. Although this illness is known as Guillain-Barré's disease, the original criteria described and insisted upon by these investigators are no longer adhered to. Careful and detailed

study of large groups of patients has revealed many variations of this symptom complex and has suggested that this illness has the capability of implicating any part of the nervous system, thus producing a variable symptomatology. It is because of the kaleidoscopic picture often presented that the actual diagnosis, particularly in the acute phases, is often fraught with dangers and inaccuracies. It is with the hope of at least pointing out some of the variations in this illness and the possible errors in diagnosis that the present review is undertaken.

It must be realized at the onset that there is no single clinical finding or laboratory test that enables one to make a diagnosis of Guillain-Barré's disease. In view of the absence of any specific etiological agent we are forced to accept a more practical attitude and to consider in the diagnosis all the features presented. It is only after a careful consideration of all the symptoms and signs that one can arrive at a final satisfactory diagnosis. This frequently will necessitate a fairly prolonged period of observation before one feels justified in classifying the illness and venturing a diagnosis.

Before pointing out the numerous pitfalls in the diagnosis of this illness, it might be well to recapitulate certain of the characterizing features. It is obvious that without a thorough knowledge of this illness, one cannot hope to avoid errors in diagnosis.

1. *A Rather Sudden Onset Occasionally Preceded by a History of Some Antecedent Infection,*

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*Chiefly of the Respiratory Tract.* Premonitory symptoms may vary from such mild complaints of malaise, backache, muscle and joint pain, mild lethargy to such acute disturbances as vertigo, severe radicular pain, headaches, acute muscle tenderness and anorexia. In many cases the illness is very slow in onset, gradually progressing over a period of months before the full-blown syndrome becomes apparent.

2. *Radicular Involvement.* This is one of the most constant features of the illness. The radicular pain is early in onset, involving chiefly the extremities. Pains may be widespread and difficult to control.

3. *Severe Muscle Tenderness.* Muscle tenderness occurs early and may persist even during recovery. Tenderness is so acute that it is precipitated by the slightest pressure.

4. *Triceps Weakness.* Regardless of the regions of the body predominantly involved by the disease, the triceps muscles seem to be implicated, resulting in severe triceps weakness even in the presence of otherwise intact muscles of the upper limbs.

5. *Facial Nerve Palsy.* Involvement of the seventh cranial nerve is present in about 30 per cent of the cases. This disturbance may be bilateral or unilateral, the latter appearing as a Bell's palsy.

6. *Absence of Those Findings Suggestive of a Septic or Toxic Reaction in Spite of the Severe Clinical Symptomatology.* The patients generally show no hyperpyrexia, leukocytosis or increased sedimentation rate. Whenever the laboratory findings indicate definite variations from normal, one must check carefully for some complicating infection.

7. *A Cell-protein Dissociation in the Spinal Fluid with a Normal Cell Count and a High Protein.* This finding even in a large series is present only in from 60 to 80 per cent of the cases. Many investigators have placed too much emphasis upon this single laboratory finding. It alone is neither pathogno-

monic nor absolutely necessary for a diagnosis of this disease. It is the dependence upon this single feature that has led to many erroneous diagnoses.

8. *Sensory Involvement.* Sensory involvement of some type associated with the motor complications is by no means constant but extremely helpful in the diagnosis. Paresthesias, hyperesthesias and anesthetics may occur. The sensory disturbances may follow a peripheral, radicular or segmental distribution.

9. *Marked Hyperirritability Often with Definite Personality Changes.* These patients often become irritable, restless and difficult to please. They tend to change from calm, composed and pleasant individuals to cantankerous, difficult patients. Definite mental symptoms are usually absent although somnolence and mild lethargy are by no means uncommon.

10. *Favorable Prognosis Usually with Fairly Good Functional Recovery.* Generally one can say that recovery is the rule regardless of the severity of the clinical picture. However, in the more severe cases fatalities do result with an over-all mortality rate of 10 per cent increasing to as high as 40 per cent in individuals over fifty years of age. Residuals may occur in the more severe cases.

Guillain-Barré's disease may affect any part of the nervous system, but the involvement tends to be accentuated in certain regions. For convenience the disease has been classified into five clinical forms, depending upon the region most severely implicated, namely, the abortive or mononeuritic form, the polyneuritic form, the myelitic form, the bulbar form and the encephalitic form. Each of these types will show scattered symptoms and findings of involvement of other regions and all have in common the characteristic clinical features of the disease described above. The pitfalls encountered in diagnosing this illness will be discussed in relationship to each of

these five clinical forms of the disease. In the illustrative cases presented in this paper the diagnosis of Guillain-Barré's disease was either made or strongly suggested by the clinical picture, but was subsequently found to be untenable and had to be abandoned in light of subsequent developments.

#### ABORTIVE OR MONONEURITIC FORM

Patients with this form of the disease complain of fleeting pains with associated muscle aching and weakness largely limited to one limb or one nerve distribution. Occasionally more than one nerve or muscle group may be involved giving the picture of multiple mononeuritis. Despite the fact that the symptoms are predominantly mononeuritic there are also scattered findings of mild weakness, reflex changes or sensory impairment which indicate a more diffuse involvement. These scattered findings may be overlooked if a careful search is not made.

The differential diagnosis includes any disorder which produces an acute mononeuritis or multiple mononeuritis (trauma, alcohol, lead, arsenic, infections, diabetes, vitamin deficiencies, etc.). A careful history of the onset of the palsy may help. Pressure palsies usually come on rather abruptly with the history of pressure on the nerve at a vulnerable spot. Generally the absence of any associated scattered neurological findings speaks against a diagnosis of Guillain-Barré's disease. A spinal cord tumor or a protruded intervertebral disc may present a difficult differential diagnosis until the passage of time establishes the correct diagnosis. As a rule, while on strict bed rest, cases of Guillain-Barré's syndrome improve while the symptoms in a cord tumor tend to be progressive.

Metastatic malignancy may simulate Guillain-Barré's disease for a considerable period. In metastatic involvement the pain is usually much more intense and per-

sistent, the course is progressively downhill and symptoms referable to other organs are often present. In a metastatic lesion the spinal fluid protein may be much higher than in Guillain-Barré's disease, often reaching as high as 1 to 2 Gm. per cent. One is most often lead astray when circumstances prevent one from obtaining an adequate history of the onset of the patient's symptoms.

Certain systemic diseases may be mistaken for the mononeuritic form of Guillain-Barré's disease. These diseases have in common a scattered and sometimes widespread involvement of the nervous system as a part of the pathologic process which implicates many organs of the body. The nervous system damage is usually secondary to the vascular, inflammatory or invasive lesions characteristic of the disease. Multiple mononeuritis, for example, is the most common neurologic complication of periarteritis nodosa and is one of the most frequent of all the symptoms of this disease. Boeck's sarcoid, dermatomyositis and metastatic malignancy may closely mimic Guillain-Barré's disease. We have recently seen a case of lupus erythematosus with widespread neuritic findings. With the exception of dermatomyositis, any of these diseases may produce encephalitic, bulbar or myelitic syndromes but most commonly produce the poly- or mononeuritic forms. The differentiation is made on the presence of some of the following findings, none of which is seen in Guillain-Barré's disease: anemia, eosinophilia, albuminuria, hematuria, skin lesions, cardiac symptoms, pulmonary findings, evidence of disease of other organs and generally a downhill course with or without remissions and exacerbations. Cell-protein dissociation may also occur in any of these systemic illnesses and cannot be used as a differentiating finding. It may be necessary to follow the course of the patient's illness over a period of time before the correct

diagnosis can be established. The following is a case illustrating this point.

CASE 1. J. G. Fifty-three year old farmer, was admitted to the hospital in April, 1946, with complaints of weakness of the extremities and pains in the chest. He considered himself to be in good health until October 11, 1945, at which time he developed a severe pain over the precordium. The patient was hospitalized for ten weeks and was treated with oxygen. While in the hospital he developed herpes zoster of the left supraorbital area and on the inner aspect of the right thigh. Following this he noted numbness and weakness of the arms and legs. These symptoms increased after discharge from the hospital, and the patient was found to have a generalized flaccid paralysis. Routine blood studies and urinalysis were normal. Spinal fluid was negative. Urine examinations for lead, arsenic and porphyrins were negative. The patient improved under physical therapy and was discharged with a diagnosis of Guillain-Barré's disease.

Two weeks before his present admission he developed a recurrence of the chest pain and the numbness and weakness of his hands and feet. He also had complaints of shortness of breath, non-productive cough, weight loss and loss of appetite. Physical examination revealed a middle-aged man who appeared chronically ill. He had scars of the old herpes zoster. The left pupil was fixed to light. Neurologic examination revealed diminution to loss of all modalities of sensation in the arms and legs. This was of a glove and stocking distribution and was more intense peripherally. There was a grade 1 to grade 2 weakness of the muscles of the extremities more marked peripherally. Tendon reflexes were markedly diminished in the arms and absent in the legs. There was a slight right facial weakness.

Blood studies now showed an anemia with a hemoglobin of 8.9 Gm., red cell count of 2,750,000 and leukocyte count of 8,000 and 13,400 on different occasions. Differential smear revealed fifty neutrophils, forty lymphocytes, one monocyte and nine eosinophils. Urinalysis was repeatedly negative. Spinal fluid showed a negative reaction and the spinal fluid protein was 48.5. Thoracentesis produced blood tinged

fluid with 3,500 leukocytes of which 85 per cent were neutrophils. Culture of this fluid was negative.

While in the hospital the patient's symptoms subsided, and he was returned home improved. Diagnosis was made clinically of periarthritis nodosa. Because of the anemia, general appearance of toxicity, cardiac symptoms, pulmonary findings, and recurrent nature of the illness the diagnosis of Guillain-Barré's disease was no longer tenable. A clinical diagnosis of periarthritis nodosa seemed warranted on the basis of the findings noted above. Early in the course of this patient's disease the findings suggested a mononeuritic form and later the picture resembled that of the polyneuritic form of Guillain-Barré's disease.

Poliomyelitis characteristically attacks scattered and isolated muscle groups and may be difficult to differentiate from Guillain-Barré's disease. This is especially true if the poliomyelitis presents itself with little fever and minimal meningeal irritation, or if the case occurs out of the usual poliomyelitis season. More commonly, however, the reverse occurs and cases of Guillain-Barré's disease are classified as atypical poliomyelitis. Usually in the latter the course is more febrile, there is more meningeal involvement, there are more cells in the spinal fluid and the involvement is predominantly of a lower motor neuron type showing no spasticity or sensory disturbances.

#### POLYNEURITIC FORM

This form is the most commonly recognized clinical type. Usually ushered in by premonitory symptoms, there is the gradual or sudden development of a flaccid paresis which generally involves the lower extremities earlier and to a greater extent than the upper limbs. The weakness is usually symmetrical and somewhat more severe in the proximal muscles. The disorder seems to have a predilection for the triceps, deltoids and extensors of wrist and fingers while the psoas, hamstrings and

peroneals are more severely involved in the lower extremities. Facial palsies are common. The musculature of the chest and abdomen becomes implicated in the severe cases. Paraesthesias, hyperaesthesias and pains are common but sensory loss is less prominent than the motor involvement. Diminution of vibratory and joint sensibility is more common than decreased superficial sensation.

Peripheral neuritis of an infectious or toxic type may be confused with Guillain-Barré's disease. Usually the former occurs in the course of some febrile illness, is distal in its distribution and remains localized to the limbs. Cranial nerve involvement is rare. Cell protein dissociation may occur.

Neuritis due to alcoholism, vitamin deficiency or diabetes should be excluded on the basis of history, examination and laboratory findings. Lead neuropathy should be considered, but the presence of lead in the urine may be misleading because painters and gardeners are in no way protected against true Guillain-Barré's disease or periarthritis nodosa. History of exposure or lead in the urine is not necessarily sufficient to establish it as the etiology of neurologic symptoms.

Post-diphtheritic paralysis may give a clinical picture which is indistinguishable from Guillain-Barré's disease. We have recently seen four patients in whom this was true. Malaria may be followed by the neurologic findings of Guillain-Barré's disease, a long recognized fact which gains new significance when evaluating neuropathies in World War II veterans. Poliomyelitis, periarthritis nodosa, disseminated lupus erythematosus and Boeck's sarcoid may resemble the polyneuritic form but have been described above.

The neurologic manifestations of acute porphyria may be identical with those of Guillain-Barré's disease. This similarity may even include cell-protein dissociation. Mental symptoms often suggest an en-

cephalitic form of Guillain-Barré's disease. There is usually a history of gastrointestinal symptoms, and there may be a change in the color of the urine. The differentiation is important because of the tendency to recurrence and the poor prognosis in acute porphyria. Gastrointestinal symptoms, recurrent paresis, mental change, and dark urine should make one alert to the possibility of an acute porphyria. The following case is presented in brief to illustrate this point:

CASE II. J. C., white male, was examined on neurologic consultation in April, 1946, with the complaints of weakness of the arms. He gave a history of the onset of abdominal pains about October 20, 1945. About November 1, 1945, the patient noted aching of his arms, back and legs. This progressed and about Christmas he complained of weakness of his arms and felt that his legs would "give out" at times. Neurologic examination revealed decreased to absent tendon reflexes in the arms with normal tendon reflexes in the legs. Strength in the right arm was normal to -2 and in the left arm -1 to -3. There was a paresis of the biceps, supinators, pronators and extensors of wrists and fingers. There was slight weakness of the right psoas and of the flexors and extensors of the toes bilaterally. Sensation was intact.

Routine urinalysis and blood count were normal. Blood non-protein nitrogen was not done. There were large amounts of porphobilinogen and uroporphyrin in the urine on qualitative tests, and a diagnosis of acute intermittent porphyria was established. Spinal fluid examination was requested but was not performed. The patient was discharged improved. He returned to the hospital August 11, 1946, with a recurrence of severe abdominal pain and died suddenly and unexpectedly two days later.

In this patient the diagnosis of acute porphyria had been established before the neurologic consultation was requested. However, other cases with less obvious gastrointestinal complaints will present greater difficulties in differential diagnosis. Any patient with symptoms of Guillain-Barré's disease who develops gastrointestinal symptoms or recurrent neurologic symptoms should be investigated for porphyria.

## MYELITIC FORM

Myelitic involvement in Guillain-Barré's disease is common and may be found in almost one-half of the cases. (Minimal pyramidal tract findings may be missed unless searched for.) The myelitic symptoms tend to come on rapidly with numbness and weakness beginning in the lower extremities. The motor involvement may be entirely flaccid or largely flaccid with some spastic elements. The tendon reflexes are usually reduced but may be hyperactive. Segmental sensory loss with a definite level is often seen. Bowel and bladder dysfunction occur early. There is usually rapid recovery with relatively little residual when compared with the severity of the symptoms at their peak.

This condition must be differentiated from the infectious myelitis occurring during the course of some febrile diseases. In the latter the onset is generally slower, the peak is reached later, the patient appears toxic and there are often severe residuals. The spinal fluid protein is usually accompanied by an elevated cell count. A vascular (thrombotic) myelitis tends to be abrupt in its onset.

The first attack of multiple sclerosis may be very difficult to distinguish from the myelitic form of Guillain-Barré's disease. The patient may relate his attack of multiple sclerosis to an antecedent upper respiratory infection. In both diseases there is a marked tendency to spontaneous recovery. The spinal fluid protein may be elevated mildly in some patients. However, Guillain-Barré's disease seldom tends to recur and following the doubtful case over a period of time should establish the correct diagnosis.

Psychoneurosis at times may simulate the myelitic or polyneuritic form of the disease. These patients may come in complaining of weakness and pains. The pains may be in the trunk or extremities and bear a re-

semblance to radicular pains. There may be hyperaesthesias and complaints of muscle tenderness. The patient's emotional instability often simulates the irritability and personality changes seen with Guillain-Barré's disease. Careful muscle testing should reveal the weakness to be more apparent than real. The reflexes are generally hyperactive in contrast to the usual diminished reflexes in Guillain-Barré's disease. Sensory examination is normal or bizarre. Spinal fluid findings are normal. Careful neurologic and psychiatric history and examination should establish the correct diagnosis. Occasionally one may have to resort to observing the patient over a period of time and to electrical testing of paretic muscles for confirmation of the clinical impression. The following case is presented in brief to illustrate this problem:

CASE III. R. C., a twenty-one year old male, was admitted to the hospital with complaints of weakness and nervousness. He gave a history of having had pneumonia three weeks previously for which he was given penicillin and sulfadiazine. During his convalescence he noted weakness, aching of the legs, and pain in the chest. He further gave a history of nervousness of several years' duration, fear of closed places, palpitation and tremor. He had been discharged from the army because of nervousness and the patient considered that he had too many illnesses to work.

Neurologic examination revealed generalized hyperactive reflexes. There was apparent generalized weakness, but careful testing failed to detect any actual weakness of any of the muscles tested. Spinal fluid examination was negative except for the total protein which was reported as 71.5 mg. per cent. Neurologic consultation failed to show any evidence of neurologic disease. An investigation revealed that due to technical error all of the spinal fluids done at that time had been reported with elevated protein levels. The erroneous report of elevated spinal fluid protein was misleading in suggesting the diagnosis of Guillain-Barré's disease.

## BULBAR FORM

Generally this type of the illness is accompanied by involvement of other parts of the nervous system, even though the bulbar symptoms do comprise the most impressive part of the clinical syndrome. Any of the cranial nerves may be implicated resulting in ophthalmoplegias, diplopia, facial anesthesia, facial palsies, dysarthria, dysphagia, etc. The latter three disturbances are by far the most frequent. In most cases there is an associated involvement of the limbs with motor or sensory disturbances. In spite of the apparently severe involvement in such a vital region the prognosis is usually good, particularly in individuals under fifty years of age. The diagnosis is generally suspected because of the afebrile course, the early facial palsy, the associated radicular involvement of the limbs and the cell-protein dissociations in the spinal fluid.

This form of the illness must be differentiated from any condition producing a bulbar palsy. Probably the most difficulty arises in its differentiation from the bulbar type of poliomyelitis. This is extremely important since the latter often carries with it a much poorer prognosis. In poliomyelitis there is usually a febrile course, signs of meningeal involvement, increase of cells in the spinal fluid and a seasonal occurrence, often with other cases in the region.

The bulbar involvement in progressive muscular atrophy, amyotrophic lateral sclerosis, arteriosclerosis, pseudobulbar palsy, causes no real diagnostic difficulties since the onset is very slow and the course generally chronic. The facial nerve is generally spared and the spinal fluid remains unchanged.

## CEREBRAL FORM

This is an extremely rare and not usually recognized type of Guillain-Barré's disease. It often begins with severe headaches,

malaise, vertigo and nausea. The symptoms may subside only to be followed by facial weakness or scattered paresis or radicular pain. After a few days the headaches again return and are accompanied by lethargy, confusion or restlessness. Papilledema is often present. The prognosis is guarded, although many patients make a fairly complete recovery.

By far the most difficult problem in these cases is their differentiation from cerebral neoplasms. Frequently the associated motor involvement suggests the focal lesions seen in brain tumors. In the presence of such a clinical picture one is often forced to resort to air studies in order to eliminate the possibility of a brain tumor. In many cases, however, careful attention to the symptomatology will suggest the proper diagnosis. In Guillain-Barré's disease the neurological findings are often scattered and accompanied by severe radicular pain. In spite of a papilledema the spinal fluid pressure is usually not greatly elevated but the protein is definitely increased.

Multiple sclerosis may also cause considerable diagnostic difficulty particularly since papillitis may also occur in this illness. A careful survey of the history, the more chronic and remitting course, the first zone colloidal gold curve, etc., all are aids in the proper evaluation of the patient.

## COMMENTS

Obviously in a brief discussion it is impossible to include all of the difficulties encountered in arriving at an accurate diagnosis of Guillain-Barré's disease. At most one can only hope to point out some of the more common diagnostic problems. With the increasing frequency with which this diagnosis is made, it becomes of extreme importance to caution against too hasty an acceptance of such a diagnosis. This is particularly true since so many illnesses, often with an entirely different



course and prognosis, may simulate the clinical picture seen in Guillain-Barré's disease.

Before completing these comments it might be well to list a group of findings which rarely occur in Guillain-Barré's disease and which, if present, should caution against such a diagnosis until careful and detailed history and investigation have eliminated every other diagnostic possibility. Even after such a study it may still be necessary to withhold a final diagnosis until the patient has been observed over a considerable period of time.

1. *Recurrences.* In most cases, usually after an acute onset, this illness becomes stationary or starts to subside. It appears that improvement, once begun, continues uninterrupted, provided moderate care and rest are obtained. Repeated relapses should make one uneasy about the accuracy of the diagnosis.

2. *Symptoms of Involvement of Other Organs.* Although systemic involvement has been described in this illness, the nervous system presents the predominant and often exclusive clinical symptomatology. Clinical evidence of involvement of other organs of the body is extremely rare in Guillain-Barré's disease.

3. *Toxicity and Fever.* The patients with Guillain-Barré's disease show almost no hyperpyrexia or signs of toxicity. In the absence of some complicating infection in the urinary or respiratory tract, such findings generally speak against a diagnosis of this illness.

4. *Protein of 1 Gm. or More.* Although Guillain, Barré and Strohl insisted on the presence of 1 to 2 Gm. of protein in the spinal fluid before justifying a diagnosis of this illness, it has been our experience that such a large amount of spinal fluid protein is extremely uncommon and when present generally suggests some other condition. Very few patients with Guillain-Barré's

disease will show a protein elevation beyond 300 to 400 mg. per cent.

5. *Meningeal Symptoms.* Signs of meningeal irritation, that is, headache, stiff neck and backache have been reported in scattered cases of Guillain-Barré's disease. In our experience this is an extremely uncommon finding and, therefore, should not be used diagnostically.

6. *Eosinophilia, Anemia, Hematuria, Albuminuria.* These findings generally suggest some systemic process with an involvement that is more widespread than the nervous system alone. Any of these findings should caution one against a diagnosis of Guillain-Barré's disease and should stimulate one to intensify his search for other etiological factors in the illness.

7. *Downhill Course.* Although the occasional patient with Guillain-Barré's disease will fail to improve, recovery is the rule in spite of the severity of the clinical picture. For this reason when a patient fails to respond, one must make a diagnosis of this illness with great caution.

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# Agranulocytosis Caused by Thiouracil\*

## *A Review of Fifty-nine Cases in the Literature and a Report of Two Additional Cases*

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THE introduction of thiouracil as an effective agent in the treatment of thyrotoxicosis has resulted in an increasing incidence of toxic reactions following the continued use of the drug. Of the reactions thus far observed by far the most serious has been the development of agranulocytosis. The application of the term, agranulocytosis, has varied considerably. Its use should be properly restricted to patients whose leukopenia is very severe and is associated with an extreme reduction or complete absence of granulocytes and whose clinical picture is usually characterized by evidence of fever, toxicity and necrotic lesions especially of the mouth and throat.

The incidence of agranulocytosis in patients treated with thiouracil averages about 1.88 per cent. (Table I.) In a report from 328 investigators,<sup>1</sup> the incidence of granulocytopenia in 5,745 patients treated with thiouracil was 168 or 2.5 per cent. This number, however, included atypical cases of simple leukopenia with neutropenia. Tyson, Vogel and Rosenthal<sup>2</sup> reported six cases of severe agranulocytosis in a small series of fifty-four cases, an unusually high incidence (11 per cent) that they could not satisfactorily explain. Of 1,091 thiouracil cases compiled from the reports of twelve clinics<sup>3</sup> there were nineteen cases of agranulocytosis, an incidence of 1.74 per cent.

In the majority of cases, agranulocytosis occurs during the second month of treat-

ment with thiouracil. Moore<sup>3</sup> found this to be true in 79 per cent of his nineteen collected cases. (Table I.) In twelve of the

TABLE I  
INCIDENCE OF AGRANULOCYTOSIS IN PATIENTS TREATED WITH THIOURACIL

Author	Series No. of Cases	Agranulocytosis	
		No. of Cases	Per Cent
Astwood <sup>4</sup> .....	62	1	1.6
Williams and Clute <sup>5</sup> .....	152	2	1.3
Williams and Clute <sup>6</sup> .....	247	3	1.2
McGavack et al. <sup>7</sup> .....	78	2	2.5
Himsworth <sup>8</sup> .....	22	1	4.5
Tyson et al. <sup>2</sup> .....	54	6	11.0
Fishberg and Vorzimer <sup>9</sup> .....	96	1	1.0
Fishberg and Vorzimer <sup>10</sup> .....	96	4	4.0
Moore <sup>1</sup> .....	1,091	19	1.74
Bartels and Blizard <sup>11</sup> .....	405	4	1.0
Lesses and Gargill <sup>12</sup> .....	62	1	1.6
Morton.....	80	2	2.5
Total.....	2,445	46	1.88

sixty-one cases reported to date (Table II), the duration of thiouracil therapy was not stated. Of the remaining forty-nine patients, thirty-one or 63 per cent developed the condition during the second month of treatment; five or 10 per cent during the first month; six or 12 per cent during the third month; and seven or 14 per cent after that time. The shortest interval between the beginning of thiouracil therapy and the onset of symptoms was one or two weeks

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TABLE II  
THIOURACIL-INDUCED AGRANULOCYTOSIS—COURSE AND TREATMENT

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
1	24	450	0	Late	?	Pentnucleotide transfusion	Died	7	M. 70. Onset WBC 1250 P37% asymptomatic 2 days—then acutely ill. Penicillin given during terminal 24 hours. <sup>13</sup>
2	7½	300	1	Late	About 225,000	Crude liver, pentnucleotide, bone marrow, transfusions	Died	5	F. 62. Complicating diabetes, thiouracil continued for 3 days after onset. Penicillin started 4th or 5th day after onset <sup>15</sup>
3	13	1,200	0	?	?	Pentnucleotide, transfusions	Recov.	11	F. 61. Angina and ulcerations after 13 wks. of thiouracil disappeared spontaneously in 6 days. Recurrence 3 wks. later. Acutely ill. Recovery followed discontinuance of drug <sup>16</sup>
4	9	850	0	?	?	Liver, transfusions	Recov.	12	F. 63. 2 days after discontinuance of drug developed inflamed nose and throat and fever. Return of leukocytes began on third day without treatment <sup>17</sup>
5	4½	3,500	0	At once	400,000	Transfusions	Recov.	13	F. 50. Headache, sore throat, enlarged glands. Temp. 104° <sup>17</sup>
6	8	2,000	19	?	?	Pentnucleotide—liver extract, sulfadiazine	Recov.	?	M. 40. Sore throat. Temp. 104° chill—acutely ill <sup>18</sup>
7	2½	2,400	4	At once	560,000	Crude liver, transfusions	Recov.	4	F. 52. Thiouracil stopped with WBC 4000, P. 45%, 36 hours later acutely ill—typical agranulocytic angina T. 104. Authors attribute rapid recovery to early intensive penicillin therapy <sup>19</sup>
8	4	1,500	0	At once	1,600,000	Liver, transfusions	Recov.	11	F. 50. The duration of thiouracil medication not clear <sup>9</sup>
9	9	4,250	5	?	?	Pyridoxine intravenously 125–200 mg. daily	Recov.	5	Authors believe pyridoxine has specific action <sup>20</sup>
10	6	360	0	?	?	Continuous sulfamerazine intravenously	Died	3	F. 49. Admitted acutely ill. Penicillin not available <sup>2</sup>
11	8	250	0	Late	680,000	Sulfadiazine	Died	4	F. 59. Acute strep. tonsillitis after 6 weeks of thiouracil. Recovery after sulfadiazine with WBC. 8650, P. 70%. After 17 days of thiouracil developed typical agranulocytic angina with fever <sup>2</sup>
12	8	500	0	At once	About 600,000	Transfusion	Died	4	F. 47. CBC. normal 3 days before admission. 2 days later acute onset with sore throat and fever. Autopsy showed necrotizing pharyngitis and toxic hepatitis <sup>2</sup>

TABLE II (Continued)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
13	10	800	0	Late	200,000	?	Died	4	F. 32. 4 days of sore throat, chills, fever and swollen glands before thiouracil stopped. T. 104, died 10 hours after admission <sup>2</sup>
14	5	3,490	1	At once	1,050,000	Liver extract, transfusion	Recov.	7	F. 29. 5 days before admission fever and sore gums and erosions T. 104-105 for 6 days, then abrupt drop. Penicillin intravenously and intramuscularly <sup>2</sup>
15	7	3,250	0	At once	400,000	Transfusions	Recov.	4	F. 50. 2 days before admission slight fever. Following day T. 102 with lesions in the mouth <sup>2</sup>
16	10	1,200	0	At once	1,000,000	Liver extract, transfusions	Recov.	6	F. 43. Sore throat, swollen gums. T. 104 for 5 days, auricular fibrillation and pneumonia. Recovery dramatic on 6th day <sup>2</sup>
17	11½	1,600	7	At once	1,250,000	Transfusions	Recov.	11	M. 58. T. 105 ulcerations of throat. WBC. on admission 1900, P. 1% <sup>2</sup>
18	4	950	6	At once	1,500,000	Transfusions	Recov.	11	M. 53. Leukopenia for 1 day then fever and angina. Desperately ill for 7 days. Peritonsillar abscess drained <sup>2</sup>
19	5	1,100	0	0	0	Sulfathiazole, pentnucleotide, liver extract	Recov.	7	M. 37. Severe pharyngitis—acutely ill. Temp. 105 <sup>4</sup>
20	6	?	?	0	0	Transfusions	Died	0	No detail of blood picture <sup>8</sup>
21	5	900	0	0	0	Pentnucleotide, liver extract, transfusion	Died	16	F. 49. Sore throat acutely ill. T. 102 treatment had no appreciable effect on blood picture <sup>21</sup>
22	?	?	?	?	?	?	Recov.	?	Patient seriously ill for several days <sup>8</sup>
23	?	?	?	?	?	?	Recov.	?	Patient seriously ill for several days <sup>8</sup>
24	8	?	?	?	?	?	Died	?	F. Agranulocytic angina. Furuncle on nose 2 weeks before. Thiouracil stopped, and paronychia 1 week prior. Terminal broncho-pneumonia and lung abscess. <sup>3</sup>
25	5	?	?	?	?	?	Died	?	F. Treated privately. Admitted to hospital with agranulocytosis and angina <sup>3</sup>
26	6	?	?	Vigorous systemic treatment			Died	10	Agranulocytosis treated apparently successfully. 4 days after blood count began to rise—patient died of cerebral thrombosis. Thiouracil stopped 10 days before death <sup>3</sup>
27	5	1,000	0	Late	400,000	Fluids	Died	5	F. 41. T. 105. Throat lesions. Died 8 hours after admission to hospital <sup>11</sup>

TABLE II (Continued)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
28	11	900	0	At once	1,315,000	Pyridoxine, crude liver	Recov.	10	F. 36. Thiouracil stopped 8 days before symptoms. Penicillin given intravenously, intramuscularly and by spray. 460,000 U. 1st day, 420,000 U. second day, etc. WBC improved 7th day. 10th day WBC 12,000 P. 50% <sup>11</sup>
29	4	1,600	7	At once	Large doses	?	Recov.	14	Penicillin dosage similar to case 28 <sup>11</sup>
30	?	?	?	0	0	0	Recov.	?	Mild agranulocytosis. Recovered without treatment <sup>11</sup>
31	4½	900	0	Late	150,000	Sulfanomides intravenously, liver extract, transfusions	Died	6	F. 56. Third course of thiouracil in 1 year. Sore throat. T. 103. Previous courses were 12 weeks and 3 weeks. Thiouracil stopped each time because of myxedema <sup>12</sup>
32	?	?	?	?	?	?	Died	?	Author mentions autopsy in case of agranulocytosis following thiouracil—no details <sup>23</sup>
33	3	400	?	Yes	?	Transfusions	Recov.	?	2 weeks after stopping drug because of leukopenia, patient developed granulocytopenia with T. 106 and cellulitis of finger <sup>10</sup>
34	28	200	0	Late	300,000 intravenously 1st day	Sulfathiazole, crude liver, transfusions	Died	4	M. 34. Sore throat. T. 105 6 days after stopping thiouracil had general malaise-admitted to hospital 2 days later. Died 52 hours after admission <sup>24</sup>
35	7	1,150	2	Late	480,000	Pyridoxine 200 mg. intravenously	Recov.	7	F. 28. Thiouracil discontinued when WBC 3250 P. 21%. 4 days later angina and fever. Author believes pyridoxine an important factor in recovery <sup>25</sup>
36	?	400	?	0	0	Pyridoxine 200 mg. intravenously	Recov.	4	2 hours after pyridoxine WBC rose from 400 to 1800 and in 4 days with daily pyridoxine 200 mg. WBC rose to 4900 <sup>26</sup>
37	?	2,000	25	0	0	Pyridoxine 200 mg. intravenously	Recov.	1	M. 28. Author found that 200 mg. pyridoxine doubled the WBC and tripled the polys. in 4 hours <sup>10</sup>
38	?	?	0	0	0	0	Recov.	13	Severe agranulocytic angina-fever-ulcerations of throat-spontaneous recovery with WBC 4500 on 13th day. Control case with case 39 <sup>10</sup>
39	?	?	0	0	0	Pyridoxine 200 mg. intravenously	Recov.	2	Similar case to above. Recovery in 48 hours following 6 intravenous injections of 200 mg. each of pyridoxine <sup>10</sup>
40	7	1,000	0	0	0	Sulfadiazine, vit. B, liver extract	Recov.	10	F. 50. Malaise and slight infection of finger. T. 104 for 5 days, few or no granulocytes for 7 days <sup>6</sup>

TABLE II (Continued)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
41	6	600	0	?	?	Penicillin, liver extract, pent-nucleotide	Recov.	12	F. 31. Sore throat for 3 days. T. 103. Infection subsided in 8 days <sup>6</sup>
42	52	1,000	0	0	0	Liver extract, pent-nucleotide. Sulfathiazole?	Recov.	12	F. 44. For preceding week patient took sulfathiazole for "infections" of skin and mouth, no complaints—no fever—refused hospitalization <sup>6</sup>
43	4	2,100	7	0	0	Pent-nucleotide, transfusions	Recov.	27	M. 57. Received thiouracil for heart failure. No lesions. (Borderline case) <sup>12</sup>
44	?	5,000	34	0	0	0	Recov.	?	F. 54. WBC dropped from 10,600 with 6% P. to 4800 with 61% P. and later to 5000 with 34% P. Sore throat. T. 100.5. Recovered on discontinuance of drug. (Borderline case) <sup>12</sup>
45	22	3,000	31	0	0	0	Recov.	?	F. 33. Sore throat, fever and granulocytopenia. (Borderline case) <sup>12</sup>
46	2	4,900	8	?	?	0	Recov.	?	Sore throat. (Borderline case) <sup>26</sup> (3 in discussion)
47	3	600	0	At once	?	?	Rec.	7	Previous thiouracil treatment 6 months ago. Severe pharyngeal manifestations. 7 days complete agranulocytosis <sup>26</sup> (3 in discussion)
48	14	750	0	0	0	Transfusions	Recov.	30	F. 47 with carcinoma of throat was given thiouracil to reduce thyroid nodes. Also had x-ray therapy. BMR was normal. Temperature normal <sup>14</sup>
49	6	?	Few	0	0	Pentnucleotide, liver extract	Recov.	?	Patient developed fever and an infected finger. Only a few granulocytes were present for 7 days <sup>27</sup>
50	1	3,900	60	0	0	Pentnucleotide	Died	?	F. 67 with heart failure responded to digitalis and sedatives—was given 0.3 gm. thiouracil by injection daily. Developed leukopenia. Responded to pentnucleotide. Following thyroidectomy died of thyrotoxic crisis <sup>29</sup>
51	?	?	?	Given	?	Crude liver extract, pyridoxine	Recov.	?	Author believes withdrawal of drug and combating concomitant infection with penicillin essential <sup>28</sup>
52	?	?	?	Given	?	Crude liver extract, pyridoxine	Recov.	?	Same as above <sup>28</sup>
53	2	?	?	?	?	?	Recov.	?	Previous thiouracil therapy; possible agranulocytosis during previous treatment at other institutions <sup>3</sup>

TABLE II (Continued)

Case	Wks. of Thiouracil	Lowest WBC	WBC Polys	Penicillin Started	Total Units	Other Treatment	Result	Days after Onset	Comment
54	4	3,100	0	?	?	?	Recov.	?	Typical pharyngeal manifestations <sup>3</sup> Concomitant sulfadiazine therapy for pneumonia <sup>3</sup> 70. Poor response to thiouracil. Also had diabetes mellitus <sup>3</sup>
55	6	?	0	?	?	?	Recov.	?	
56	6	?	?	?	?	?	Recov.	?	
57	7	?	?	?	?	?	?	?	No details <sup>3</sup>
58	8	?	?	?	?	?	?	?	Concomitant sulfathiazole therapy. No details <sup>3</sup>
59	36	?	?	?	?	?	?	?	No details <sup>3</sup>
60	1	750	0	Late	1,100,000	Pyridoxine, transfusions	Died	14	F. 63. Third course of thiouracil. This report. Details in Table III
61	7	1,000	0	At once	2,250,000	Pyridoxine, liver extract, transfusions	Recov.	11	F. 33. This report. Details in Table IV

(Cases 46, 53, and 61, Table II) (at least two of these three patients had had previous thiouracil therapy) and the longest interval was fifty-two weeks. (Case 42, Table II.)

It is the time element even more than the dosage of thiouracil that determines the possible occurrence of agranulocytosis.<sup>1</sup> The unpredictable nature of this dreaded complication allows no warning of bone marrow depression before the onset of symptoms except by hematologic examination. The importance of close and careful supervision of the white blood count, particularly during the "dangerous" second month, cannot be overemphasized.

The age and sex of the patient are apparently not important factors in agranulocytosis. The youngest patient was twenty-eight years and the oldest seventy years. Of the thirty-seven cases in which there is a record of sex, twenty-nine were women and eight men—a ratio of about  $3\frac{1}{2}$  to 1. This closely approximates the incidence in the sexes of the underlying hyperthyroidism for which the thiouracil was administered.

Seventeen of the sixty-one patients died from agranulocytosis. This high mortality

rate (28 per cent) emphasizes the need for earlier recognition and more effectual treatment.

In the present series of eighty patients treated with thiouracil for thyrotoxicosis, two developed agranulocytosis.

#### CASE REPORT (TABLE III)

L. W., a sixty-three-year old white female, had been under medical care for thyrotoxicosis for the past four years. Since January, 1945, she had been treated with thiouracil. On April 7, 1945, the patient developed a slight sore throat and four days later the white blood count was "very low" with a complete absence of granulocytes. At a previous date the patient had had a similar attack of agranulocytosis that had responded to some undetermined treatment. She was first seen by us April 16, 1945, when admitted to the hospital complaining of sore throat, fever and cough.

Examination revealed an acutely ill patient with temperature of 100.6°F., pulse 140 and irregular, and respirations 36. The throat was inflamed, the tonsils cryptic and covered with exudate. The thyroid was enlarged and firm. Auricular fibrillation with a rate of 160 was noted. No murmurs were heard. The blood pressure was 160/90. Moist coarse râles were

TABLE III

Date	Hb.	RBC.	WBC.	Per Cent Polys.	Medication	Comments
4/16	90	4,350,000	5,200	40	Digitalis gr. $\frac{1}{2}$ t.i.d. oxygen sedation	Patient admitted acutely ill. T. 100.6 P. 140. R. 36 sore throat, cough, thyrotoxicosis—congestive heart failure
4/18	..	.....	3,600	51	500 cc. blood—pentnucleotide 20 cc., Lugol's mx t.i.d. vitamins	BMR. +63%
4/20	..	.....	11,100	75	Stilbestrol 5 mg. twice daily	Attempt to reduce thyrotropic factor by inhibiting anterior pituitary
4/21	..	.....	13,400	85	Aminophyllin. Phenobarbital	
4/23	..	.....	12,800	91	Lugol's solution discontinued	X-ray shows cardiac enlargement. No pulmonary congestion
4/24	..	.....	14,200	81		
4/27	95	5,050,000	27,600	84	.....	BMR +49%. Patient better. Heart rate 92 with no deficit. Surgeons suggest thiouracil
5/1	89	.....	18,400	85	Transfusion 250 cc.	
5/2	91	4,850,000	13,500	72	Transfusion 250 cc.	
5/3	90	5,270,000	22,100	89		
5/4	..	.....	25,000	90		
5/15	84	4,490,000	16,400	90		
5/7	83	4,550,000	9,700	83		
5/8	80	4,550,000	8,200	77		
5/9	83	4,300,000	26,000	91	.....	Surgeons found patient to be a very poor surgical risk. Suggested x-ray therapy
5/10	80	4,320,000	11,300	75	.....	X-ray consultation. X-ray therapy inadvisable
5/11	..	.....	16,000	82		
5/12	..	.....	13,000	76		
5/15	75	4,050,000	11,400	69	.....	BMR +76%. Lost 4 lbs. in past 4 days
5/16	78	3,780,000	12,200	81		
5/17	78	4,100,000	10,000	73		
5/18	73	4,310,000	9,900	70		
5/21	78	4,250,000	5,700	67		
5/22	..	.....	5,900	77	.....	BMR +100%. Test not satisfactory. Clinically patient's condition poor
5/23	..	.....	6,900	74	Thiouracil	Thiouracil started 0.4 Gm. every 6 hours, first day. Then 0.1 Gm. 5 times daily. All other medication stopped
5/25	..	.....	8,400	82		
5/28	83	4,300,000	8,700	82		
5/29	75	4,450,000	4,200	57	Thiouracil discontinued. Pyridoxine, intravenous fluids	Medication stopped. X-ray shows cardiac enlargement
5/30	75	4,600,000	3,000	28	Pyridoxine 200 mg. intravenously	Sore throat
5/31	78	4,290,000	1,000	11	Fluids. Pyridoxine 200 mg. I.V.	Inflammation more marked
6/1	80	4,300,000	1,350	0	Penicillin 20,000 units every 3 hr. Pyridoxine 200 mg. intravenously	Surgical consultation. BMR +77%
6/2	..	.....	750	0	Pyridoxine. Penicillin	ENT consultation. Severe pharyngitis and tonsillitis with ulcerations
6/3	..	.....	2,100	0	500 cc. blood. Pyridoxine 200 mg. Penicillin I.V.	Surgical consultation. Too ill for surgery
6/4	..	.....	1,800	1	Penicillin. Pyridoxine 200 mg. I.V. Stilbestrol I.V. 10 mg.	Patient's condition still critical
6/5	..	.....	1,450	2	Oxygen. Penicillin. Pyridoxine 200 mg. Blood transfusion.	Severe secondary infection of throat. T. 103°F., P. 140, R. 40
6/6	..	.....	5,000	16	Oxygen. Penicillin. Pyridoxine 200 mg. Blood transfusion	Portable x-ray shows fluid in pleural space and bronchovesicular congestion. Patient sinking. Died 10.30 P.M. Total penicillin 1,100,000 units



present in both lung bases. The liver was felt two and one-half fingers below the coastal margin and pretibial edema was present. Rapid digitalization was started and oxygen and sedation were given. The electrocardiogram confirmed the auricular fibrillation with rapid ventricular rate. X-ray of the chest revealed enlargement of the cardiac shadow and bronchovesicular congestion. The white cell count on admission was 5,200 with 40 per cent polymorphonuclear cells.

The following day she seemed somewhat improved. She was given 500 cc. of whole blood, vitamins B and C intravenously, pentnucleotide 10 cc. twice daily, morphine sulfate as needed and she was started on Lugol's solution m. 10 three times daily. The basal metabolic rate was +63 per cent. The following day, the white cell count was 3,600 with 51 per cent polymorphonuclear forms of which eighteen were immature. She seemed clinically better, however. Two days later, on her sixth hospital day the white count rose to 11,100 with 75 per cent polymorphonuclears. This was thought to be the "leukocytic hyper-reaction" following agranulocytosis. Lugol's solution was stopped and patient was given 5 mg. stilbestrol twice daily. By April 27th she was clinically much better. The pulmonary congestion was gone. The heart rate was 92 with no deficit. The basal metabolic rate was plus 49 per cent. The laboratory findings were as follows: Blood sugar 153.8 mg. per 100 cc., creatinine 1.2 mg. per 100 cc., creatine 8.58 mg. per 100 cc. or 19.7 mg. in twenty-four hours, cholesterol was 234 mg. per 100 cc. and esters 82.5 mg. per 100 cc. The urine showed a faint trace of albumin. The Wassermann was negative as was the galactose tolerance. The prothrombin time was 26.1 seconds. By April 27th, the fasting blood sugar was 126 mg. per 100 cc. and cholesterol 207 mg. with cholesterol esters 62. The cephalin flocculation test was 1+. The basal metabolic rate was +49 per cent.

The patient's white count remained high and she was increasingly nervous. On May 12th, the basal metabolic rate was +76 per cent and her weight had gone down 4 pounds in as many days. The advisability of x-ray therapy arose but on consultation it was believed that the patient's generally poor condition and her tend-

ency to agranulocytosis would make the amount of radiation necessary to control the hyperthyroid state dangerous. In the absence of malignancy and pressure symptoms, x-ray therapy was not advised. The patient did not do well and on May 22nd the basal metabolic rate was +100 per cent. Although unquestionably a good part of her high rate was due to the cardiac decompensation, the thyrotoxicosis was severe. At this time the cholesterol was 128.7 mg. per 100 cc. and the cholesterol ester fraction was 82.5. With definite misgivings thiouracil was started on May 23rd (as noted in Table III). At this time the white cell count was 6,900 with 74 per cent polymorphonuclears. On May 28th, the white cells were 8700 with 74 per cent polymorphonuclears. The following day the count dropped to 4,200 with 57 per cent polymorphonuclears. The thiouracil was stopped at once and patient was given 1,000 cc. of 10 per cent glucose immediately and 100 mg. of pyridoxine intravenously twice daily. The following day, May 30th, the white count dropped to 3,000 with 28 per cent polymorphonuclears. The pyridoxine and infusions were continued. A sore throat had developed but no ulcerations were seen. The next day the white count dropped to 1,000 with 11 per cent polymorphonuclears. On June 1st, the leukocytes were 1350 but there was a complete absence of granulocytes. The basal metabolic rate was +77 per cent. She was started on penicillin 20,000 units every three hours and the pyridoxine, 200 mg. intravenously daily, was continued. The surgeons agreed to operate as soon as the agranulocytosis cleared up. The otolaryngologist found a severe pharyngitis and tonsillitis with ulcerations of the throat and advised continued use of penicillin. On June 2nd, the white count rose to 2,100 and the patient was given 500 cc. of whole blood. The following day granulocytes began to appear in the circulating blood. The patient was still acutely ill with a severe secondary infection in the throat. The temperature was 103°F., pulse 140, and respirations 40. The pyridoxine and penicillin were continued. On June 6th, the white count rose to 5,000 with 16 per cent polymorphonuclears but clinically the patient was very low. She was given another transfusion and infusion and continuous oxygen.

TABLE IV

Date	Temp.	Pulse	Resp.	Hb.	RBC	WBC	Polys.	Comment
2/21	.....	74	..	80	4,000,000	6,750	68	Patient has been receiving 4 Gm. thiouracil daily since 1/9/46. White cell count has been normal. BMR +25%
2/28	.....	96	..	78	3,750,000	3,950	0	Patient left before blood count was determined and could not be reached. BMR +14%. Thiouracil 0.3 Gm. daily stopped by telephone
3/1 A.M.	98.6	90	20	77	.....	2,250	0	Patient was given 50,000 U. penicillin and admitted to hospital. On questioning complained of very slight sore throat
3/1 P.M.	98.6	90	20	75	4,400,000	1,050	0	Sore throat, small ulceration of palate and gums. Blood transfusion (500 cc). Saline, penicillin 25,000 U. every 3 hours
3/2 A.M.	100	76	20	99	4,510,000	1,000	0	Folic acid 50 mg. daily. Pyridoxine 25 mg. daily intravenously, crude liver 2 U. every 2 days. Fluids-high vitamin diet. Persistent sore throat. Penicillin 200,000 U. daily
3/2 P.M.	101.4	90	20	80	4,500,000	1,250	2?	Lymphocytes ranged from 89 to 96%. Monocytes 1-4%. Clinical condition same. Not acutely ill
3/3	102.4	110	20	93	4,640,000	1,350	0	Patient complained of soreness of throat and neck. Painful to open mouth. Not toxic
3/4	102	100	20	89	4,880,000	1,300	0	Receiving same medication
3/5	101	90	20	82	4,630,000	1,100	0	Patient comfortable
3/6	100	90	20	84	4,400,000	1,300	0	Folic acid and crude liver extract discontinued. Penicillin 200,000 U. daily as before
3/7 A.M.	100	90	20	85	4,750,000	200	0	Pyridoxine discontinued. 3 Plasma cells, 1 metamyelocyte per 100 cells seen
3/7 P.M.	98.6	84	20	..	.....	2,700	3	3 immature polymorphs noted, 2 metamyelocytes, 3 transitional cells, 84 lymphocytes, 8 monocytes. Penicillin only medication
3/8	97.6	80	18	88	4,770,000	4,000	14	14 polys of which 9 were immature, 4 myelocytes, 1 metamyelocyte, 3 transitionals. Throat very slightly sensitive. Ulcerations healing
3/9	97.6	80	18	89	4,900,000	6,200	21	Mouth and throat much better. No complaints
3/10	98	80	18	85	4,310,000	9,450	34	20 immature cells. 60 lymphocytes. No symptoms—throat clear
3/11	94.4	78	18	90	4,750,000	11,600	46	Penicillin stopped. Patient discharged in good condition
3/16	.....	84	..	90	4,400,000	11,100	54	Patient feels fine
3/29	.....	80	..	83	4,150,000	12,200	65	No complaints

Despite all measures she kept sinking rapidly and expired that night at 10:30 P.M. In all she had received 1,600 mg. of pyridoxine intravenously and 1,100,000 units of penicillin.

#### CASE REPORT (TABLE IV)

E. K., a thirty-three year old housewife, complained of palpitation, increasing nervousness, fatigue and loss of weight. A subtotal thyroidectomy had been performed twelve years earlier for similar complaints. Several months prior to our seeing her, she had observed an increase in the size of a small mass in the neck. This had been present since 1941 at which time

her basal metabolic rate was -4 per cent. Examination in October, 1945, revealed a highly nervous individual with a pulse of 104, blood pressure 100/70 and basal metabolic rate +26 per cent. Her weight was 97½ pounds. She did not respond to sedation and on January 9, 1946, thiouracil therapy was started.

After seven weeks of uneventful treatment, the patient's leukocyte count suddenly dropped to 3,950 cells per cu. mm. with a complete absence of granulocytes. Subjectively there were no complaints. The patient could not be reached until the following morning when the white

blood count had fallen to 2,250 with a complete absence of polymorphonuclear forms. She was given 50,000 units of penicillin and 2 units of crude liver extract. On admission to the hospital immediately thereafter she still felt perfectly well. However, that afternoon she developed a slight sore throat and scattered small ulcerations on the palate. Five hundred cc. of whole blood and 500 cc. of saline were given that day. Twenty-five thousand units of penicillin were administered every three hours. Folic acid, 50 mg. orally, pyridoxine 25 mg. and crude liver extract 2 units intramuscularly were given daily. The first day in the hospital the white blood cells dropped to 1,050 and the following day to 1,000 per cu. mm. By the third day the temperature rose to 102.4°F. and the lesions in the mouth, especially the ulcerations of the lower gum, increased in size and number. The cervical adenopathy was marked. The patient did not appear toxic, however, and complained only of moderate soreness in the mouth and neck. By the seventh day the temperature had dropped to normal, the white cell count had increased to 2,700 and immature granulocytes began to appear. Folic acid and pyridoxine had been discontinued the preceding day. The lesions healed rapidly so that by the eleventh hospital day the patient was discharged as cured. She had received a total of 2,250,000 units of penicillin. The mild reactive leukocytosis (11,600 with 46 per cent polymorphonuclear forms on discharge) persisted for about three weeks.

#### COMMENTS

With the increasing use of thiouracil in the treatment of hyperthyroidism, it is inevitable that additional cases of agranulocytosis will be encountered. Because this serious complication usually makes its appearance with disconcerting suddenness, its early diagnosis is of extreme importance. During the period from the third to the twelfth week of therapy, when 85 per cent of the cases occur, the possibility of agranulocytosis must be anticipated and carefully guarded against. Unfortunately, even frequent blood counts may not give sufficient

warning. Any untoward change in the white cell count, whether it be a gradual diminution in number or a decrease in the granulocytes or even a moderate unexplained leukocytosis (the irritation before the depression of the bone marrow) should call for added caution. The patient should be advised that the slightest evidence of toxicity, such as the mildest sore throat, rise in temperature or malaise warrants notifying his physician immediately and discontinuing the drug until further instruction is given.

With the occurrence of agranulocytosis, the prompt discontinuance of the offending drug and the immediate institution of adequate treatment is essential to recovery. In some instances (Table II, Cases 3, 4, 30, 38, 44, 45) more or less prompt regression of untoward effects followed termination of the medication. Because of the unpredictable course of this disease, such a limited regimen is fraught with danger. In many cases (Table II, Cases 1, 4, 7, 28, 33, 35, 61) the acute onset of symptoms occurred several days following the cessation of medication. To withhold early and intensive treatment because the patient is asymptomatic may result in disaster. (Table II, Case 1.)

Penicillin is by far the most valuable agent used in combating the dangers of agranulocytosis. Patients who succumb to agranulocytosis die, not from the lack of granulocytes *per se*, but from the overwhelming sepsis that results from the slightest secondary infection. The value of penicillin lies in preventing or controlling the secondary infection until the bone marrow recovers and spontaneous regeneration of the granulocytes occurs. This usually takes about six or seven days.

Penicillin must be given immediately upon diagnosis and in adequate dosage. In the report of the Council on Pharmacy and Chemistry<sup>1</sup> 500,000 units per day was rec-

commended as the most effective treatment for agranulocytosis. This dose exceeds that given any of the patients listed in Table II. Of the ten cases in which penicillin was given early and in doses of 100,000 units or more daily, only one patient died. (Table II, Case 12.) It is conjectural whether this death might have been avoided by larger doses.

The value of other supplementary treatment should not be minimized. The use of pyridoxine is gaining increasing popularity with some workers. Cantor and Scott<sup>20</sup> believe that pyridoxine is the liver factor responsible for the granulocytopoietic effect in agranulocytosis. They also believe that pyridoxine is the factor involved in maturation and emigration of polymorphonuclear cells. (Table II, Case 9.) Fishberg and Vorzimer<sup>10</sup> treated three patients with agranulocytosis with pyridoxine intravenously. (Table II, Cases 36, 37, 39.) They found that an intravenous injection of 200 mg. of pyridoxine was accompanied by doubling of the white cell count and tripling of the polymorphonuclear cells within four hours. A patient in a control test (Table II, Case 38) required thirteen days to recover. They concluded that pyridoxine hastens recovery by bringing about a rapid and significant rise in circulating granulocytes. Wilson<sup>25</sup> also believes that pyridoxine played an important part in the cure of his patient. (Table II, Case 35.) However, valuable as this agent may be in shortening the time of absence of the granulocytes from the blood stream, it must be remembered that the significance of this absence lies in the lowered leukocytic defense of the body against infection. Penicillin, we strongly believe, can prevent infection or control its spread during this period of agranulocytosis, whether it be a day or a week.

The value of other agents used, such as folic acid, pentnucleotide, yellow bone marrow and crude liver extract, has not

been satisfactorily demonstrated. These agents, if used, should be employed only as adjunct treatment. Most workers use whole blood in the treatment of agranulocytosis. The value of this procedure is unquestioned provided the transfusions are not repeated so frequently as to cause reactions.

The sulfonamides, at times themselves injurious to the bone marrow, should not be used if penicillin is available.

The course of the acute stage of agranulocytosis usually runs about a week. In many cases recovery has been rather dramatic. After days of high temperature and severe toxicity, the patient may awaken on the fifth, sixth or seventh day subjectively and objectively greatly improved, with hematologic evidence of leukocytic regeneration.

Of the seventeen fatalities recorded, ten patients (Table II, Cases 1, 2, 10, 11, 21, 24, 27, 31, 34, 60) either did not receive penicillin or received it late in the disease; in three cases (Table II, Cases 2, 13, 24) thiouracil was continued for several days after the onset of symptoms; in four cases (Table II, Cases 20, 25, 26, 32) little or no details were given.

One patient (Table II, Case 12) has been discussed above. Another patient (Table II, Case 50) recovered from a mild leukopenia but died postoperatively from thyroid crisis. This case is not considered a drug fatality but is included because the author<sup>29</sup> believed that death was due to an uncompensated granulocytopenia. The patient in our series (Table II, Case 60) was critically ill at admission and, although included as a drug fatality, probably would have died from the underlying thyrotoxicosis and heart failure.

#### SUMMARY

Fifty-nine cases of thiouracil-induced agranulocytosis collected from the literature and two additional cases herewith reported are analyzed and discussed.

The importance of early diagnosis and prompt institution of treatment is stressed.

Penicillin, given early and in massive doses, has been found to be the most effective agent in the treatment of the complications of agranulocytosis.

Adjunct treatment, especially the administration of whole blood and pyridoxine may be of considerable value in hastening the recovery.

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# Seminars on Rheumatic Fever

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VOLUME II of The American Journal of Medicine will contain twelve stenographic reports (edited for publication) of seminars on rheumatic fever conducted at the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, New York. The speakers included recognized authorities in the field of rheumatic fever and rheumatic heart disease. The audience who participated in the discussions included general practitioners, pediatricians, cardiologists, public health officers, nurses, and social workers. The symposium was sponsored, in part, by the Nassau County Tuberculosis and Health Association, by the J. and G. Eisenberg Foundation, and by Mr. P. Brenner.

The program follows:

## EPIDEMIOLOGY OF RHEUMATIC FEVER

Dr. John R. Paul, *Yale University School of Medicine*

## PATHOLOGY OF RHEUMATISM

Dr. William C. Von Glahn, *Bellevue Hospital and New York University School of Medicine*

## RELATIONSHIP OF THE HEMOLYTIC STREPTOCOCCUS TO RHEUMATIC FEVER

Dr. Homer Swift, *Hospital of the Rockefeller Institute of Medical Research*

## HEREDITY AND RHEUMATIC DISEASE

Dr. May Wilson, *New York Hospital and Cornell Medical School*

## CLINICAL MANIFESTATIONS OF RHEUMATIC FEVER

Dr. T. Duckett Jones, *House of Good Samaritan and Harvard Medical School*

## RHEUMATIC HEART DISEASE IN THE ADULT

Dr. Cary Eggleston, *New York Hospital and Cornell Medical School*

## LABORATORY AND CLINICAL CRITERIA OF RHEUMATIC FEVER IN CHILDREN

Dr. Leo M. Taran, *St. Francis Sanatorium for Cardiac Children, Roslyn, L. I., N. Y.*

## DIAGNOSTIC VALUE OF ROENTGENOGRAPHY AND FLUOROSCOPY IN THE DIAGNOSIS OF RHEUMATIC HEART DISEASE

Dr. J. B. Schwedel, *Montefiore Hospital, New York*

## ELECTROCARDIOGRAPHIC FINDINGS IN RHEUMATIC HEART DISEASE

Dr. Harold E. B. Pardee, *Cornell Medical School*

## TREATMENT OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN CHILDREN

Dr. Leo M. Taran, *St. Francis Sanatorium for Cardiac Children, Roslyn, L.I., N. Y.*

## THE RÔLE OF THE MEDICAL SOCIAL WORKER IN THE PROBLEM OF MANAGEMENT AND CONTROL OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Miss Grace White, *The New York School of Social Work, Columbia University*

## THE PUBLIC HEALTH ASPECTS OF RHEUMATIC FEVER

Dr. H. S. Mustard, *Columbia University School of Public Health*

# Epidemiology of Rheumatic Fever\*

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NEW HAVEN, CONNECTICUT

I AM grateful for the opportunity to come to this institution and to see the excellent and extensive work that has been going on here for a number of years. I am impressed by how much carefully collected information has been accumulated here regarding the important disease which we are to discuss in this seminar. It is also a great personal pleasure for me to be here and to be one of the distinguished group that has been assembled for this series of seminars. I feel humble about it because I am not an authority on rheumatic disease.

One needs only to compare today's knowledge with that of twenty years ago to realize how far we have come in learning about rheumatic fever. When I was a medical student, and that was not long ago, rheumatic fever was regarded as a wholly mysterious disease. We knew something of the Aschoff body, which was considered a unique finding in medicine and one which must be associated with a unique cause. The mysterious character of rheumatic fever as we knew it then, struck terror into the heart of the medical student. Impressions of the nature of rheumatic fever went little further than the old statement by Lasègue, that it was a disease which, "licks the joints and bites the heart."

Since then, in spite of many unsolved problems in this disease, we no longer consider it wholly mysterious. Progress has been made in England and on the European continent, but particularly in the last two decades has work been done in this country. This includes the work of Dr. Homer F. Swift, Dr. Alvin F. Coburn, Dr. T. Duckett Jones, and others, which will, I am sure,

be discussed in subsequent sessions of this series of seminars.

Although I plan to limit this discussion to the epidemiology of rheumatic fever, we may include a few words on pathogenesis. We know, of course, that the relationship of rheumatic disease to sore throats has been recognized at least as far back as the early 1880's. It is now well recognized that a sore throat precedes, in most instances, an acute attack of rheumatic fever. But this relationship of sore throats to rheumatic disease is not a simple one, nor is it well described by calling the sore throat a "focal infection." At least, we cannot eradicate rheumatic fever by tonsillectomy, or by removing certain foci. The concept of focal infection as an explanation of the disease was eventually given up.

About the year 1930, the work of Schlesinger in England, and Coburn in this country, indicated that rheumatic fever is often preceded by a particular type of infection, namely, infection caused by the hemolytic streptococcus. This concept has developed over a period of the last fifteen years and we have now reached the stage where we can say, with a fair degree of certainty, that from the epidemiologic standpoint, and perhaps also from the immunologic standpoint, rheumatic fever is in some way related to infection caused by hemolytic streptococci.

The clinical relationship of events preceding a rheumatic attack (Fig. 1) is demonstrable in about one-half of the cases. An acute streptococcal infection, known as phase 1, initiates this sequence. It does not have to be severe and often escapes notice.

\* From the Department of Preventive Medicine, Yale University, School of Medicine. Read at St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, October 2, 1945

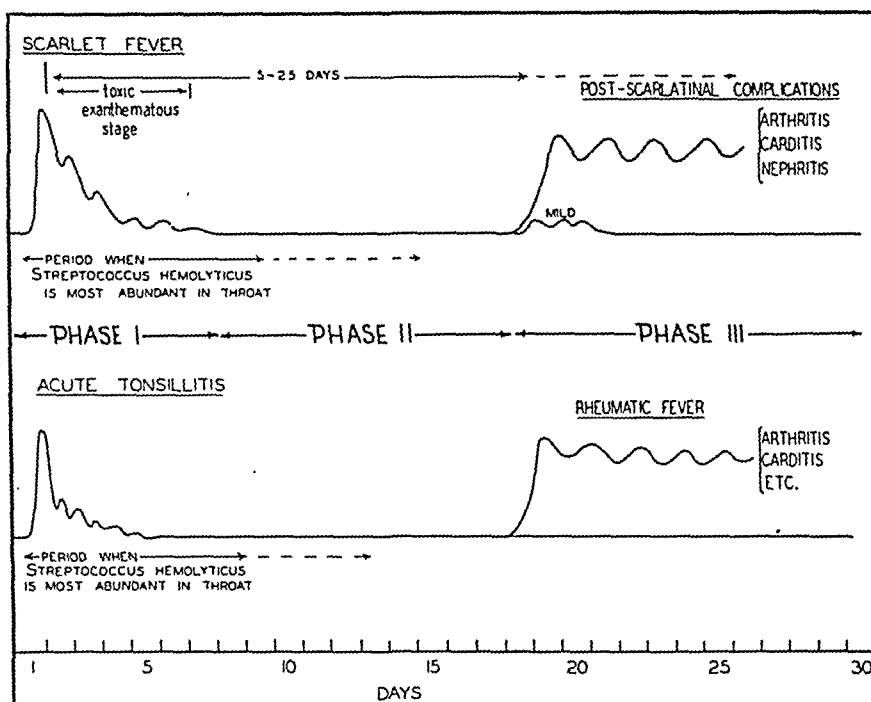


FIG. 1.\* Diagrams modified from Escherich and Schick to illustrate the possible forms indicated by temperature curves which the non-suppurative "complications" of scarlet fever and of acute tonsillitis may assume. The division of this process into three phases is also shown.

There may follow a quiescent period, or latent period, lasting anywhere from five to twenty-one days. This is known as phase 2. This in turn is followed by a third phase, which is the period during which rheumatic fever manifests itself. This recalls the events originally observed in the non-suppurative complications of scarlet fever by Escherich and Schick. Here the toxic exanthematous stage is also followed by a quiescent period lasting anywhere from five to twenty-five days, which in turn may be followed by post-scarlatinal complications, such as arthritis, carditis and nephritis. As in scarlet fever, however, it is obvious that only in a small percentage of cases of acute tonsillitis does an acute rheumatic attack subsequently develop.

This "explanation" of the events leading up to rheumatic fever is not final. It neglects the possibility that reinfection by multiple strains of streptococci may also play

some part. But that is theoretical and not final either.

A classic example of rheumatic disease following hemolytic streptococcal infection is presented by a milk-born epidemic in Denmark in the year 1926. (Fig. 2.) It appears from this chart, that this epidemic began at the end of November and rose to the peak in a few days. About three weeks after the peak of this epidemic of hemolytic streptococcal infection, cases of rheumatic disease made their appearance and the incidence of such cases increased for the next two or three weeks. This type of sequence has been seen both here and in other countries over and over again. Such experiences were common in military installations in this country during the war.

The repeated occurrence of streptococcal sore throat epidemics followed by increasing incidence of rheumatic disease is strong evidence of a relationship between the two. Most of the epidemics of rheumatic fever that have been reported, have apparently

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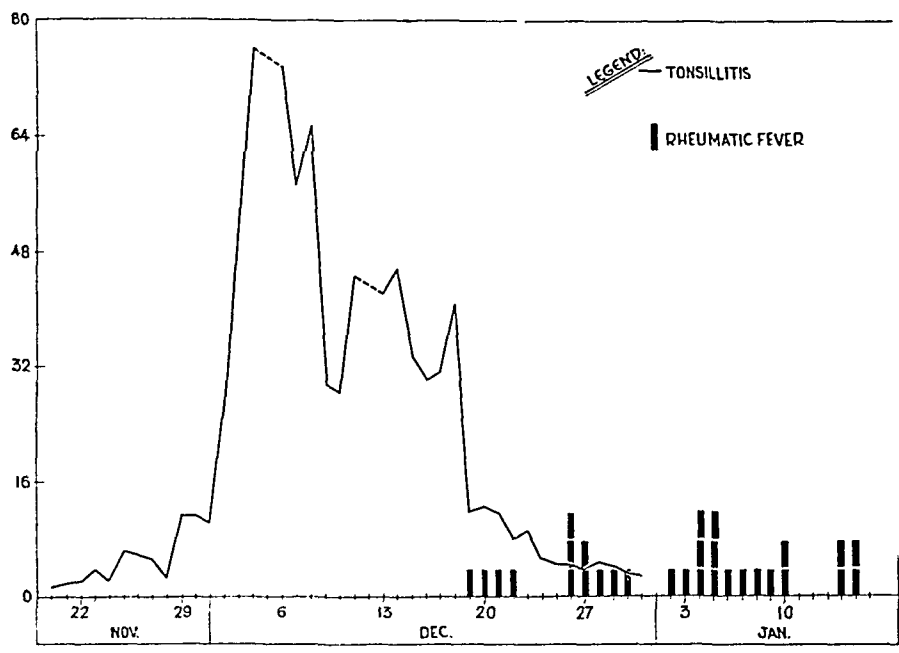


FIG. 2. Severe milk-borne epidemic of hemolytic streptococcal infection which occurred in Denmark in 1926. The scale on the left indicates the daily number of cases of tonsillitis. Late in the epidemic, thirty cases of rheumatic fever appeared. (From Madsen and Kalbak. *Acta. path. et microbeal. Scandinav.*, 17: 305, 1940.)

followed epidemics of streptococcal infections, and from all this it becomes apparent that a “good” year for hemolytic streptococcal infections is a “good” year for rheumatic fever.

Much can be learned about this disease from observing families, as was done in the study represented in Figure 3. Here we see that five members of the same family have suffered an acute attack of streptococcal infection. Their illnesses began about the same time: one member with an acute sore throat followed by otitis media; another with a scarlatina form rash at the time of the acute infection; a third member with a long attack of tonsillitis which subsided without sequellae in a week or ten days, and a fourth member with tonsillitis of short duration; a fifth member had a sore throat which was followed by a latent period of several days and subsequently, by a rheumatic attack.

Thus, it is apparent that this same type of initial infection may manifest itself in different ways in different members of the

same family. In some families there is stronger predisposition to rheumatic fever than others, the susceptibility for rheumatic attacks following streptococcal illness being apparently greater than in other families.

The multiple courses that the disease may take from its onset will not be discussed here. No doubt, this will be covered by various other members of the seminar. But let us turn now to the size of the problem in this country. Where does it flourish best and what are the geographic and sociologic factors which encourage its spread? What are the circumstances under which it is most prevalent?

Type A streptococcal infection may be food-borne or milk-borne, but there is no special vector or medium such as the mosquito, or the louse, necessary for the transfer of the infection from one person to another. In other words, it is a crowd disease, and a contact disease, similar to many of the respiratory infections. Crowded dwellings or the herding together of susceptible children or adults leads to the spread of

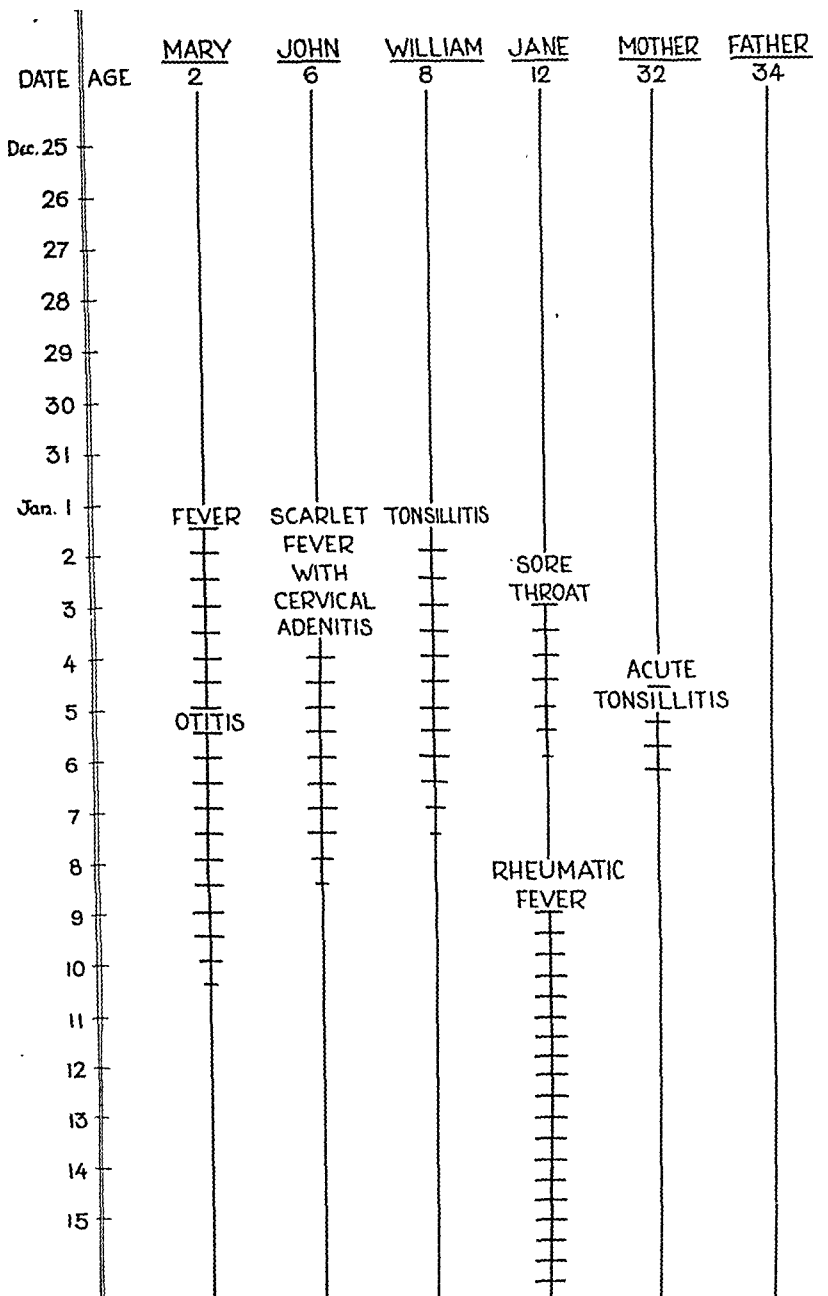


FIG. 3. A family composed of two parents and four children in which an epidemic of acute hemolytic streptococcal infection occurred. In each individual the disease expressed itself in a different form. One finds that in infancy and young childhood hemolytic streptococcal infections are often a long disease (three to six weeks) accompanied by suppurative complications. This may be in some contrast to the shorter (and more acutely prostrating) disease which is more characteristic of late adolescence and young adult life. In one child (Jane) the streptococcal illness was followed by rheumatic fever.

such infection; as for instance, the sharp increase of upper respiratory infections when school opens.

It is not easy to determine the prevalence

of rheumatic disease. It is not a reportable disease in most parts of this country. Attempts have been made to make it reportable in some United States cities,

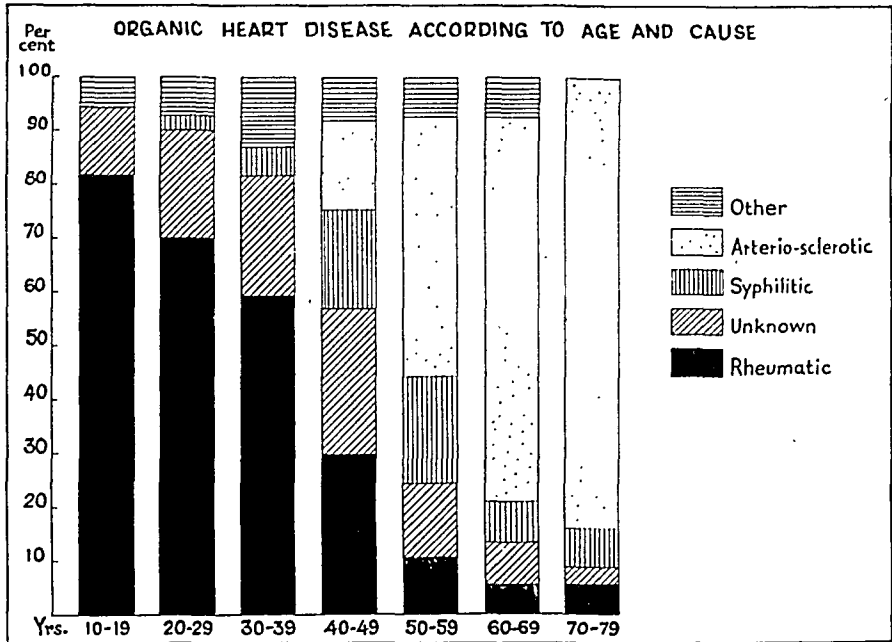


FIG. 4. Relative frequency of different types of organic heart disease at different ages. The sample consists of 1,001 cases, of which 85.4 per cent were clinic patients (Cardiac Clinic for Adults, Bellevue Hospital, New York City) and 14.6 per cent private patients from the practice of the late Dr. John Wyckoff, of New York City. (From Wyckoff and Lingg. *Am. Heart J.*, 1: 446, 1926.)

but so far without much success. The reason for this failure is apparent. Even the physician himself is not yet convinced why he should report rheumatic fever since it is not really evident to him that by so doing he may protect the community. Furthermore, it is difficult to be certain of the diagnosis and the physician often does not want to commit himself by reporting questionable cases to the Health authorities. He cannot rely on established laboratory tests such as exist in syphilis or tuberculosis, for instance. Perhaps we should rather make *rheumatic heart disease* reportable instead of *rheumatic fever*. Here we are on somewhat surer ground with regard to diagnosis. Much education and thought on this subject is still necessary.

We can learn more from mortality than from morbidity statistics. These, too, however, are variable. Nevertheless, *most children who die of heart disease, die of rheumatic heart disease*. Some, of course, die of congenital heart disease but it is established that fully

80 per cent of deaths from heart disease in children under fifteen years of age are due to rheumatic heart disease. (Fig. 4.) If then, we study the prevalence of juvenile cardiac mortality, we obtain a fair estimate of the prevalence of rheumatic fever in general. In this way, we have gotten some notion as to how extensive this disease is.

From hospital admission figures, we can also learn something about the prevalence of rheumatic fever by determining what proportion of admissions to the medical or children's wards have rheumatic disease. This proves to be from 1 to 5 per cent of the patients on the general medical service. As far as hospital admissions are concerned, a ten-year study at the New Haven Hospital (1929-1938) showed that cases of rheumatic fever, both active and inactive, constituted the third largest number of admissions for "infectious diseases." (Fig. 5.) Tuberculosis heads the list, syphilis stands second, and rheumatic fever third. Even if only the active cases are included, one is

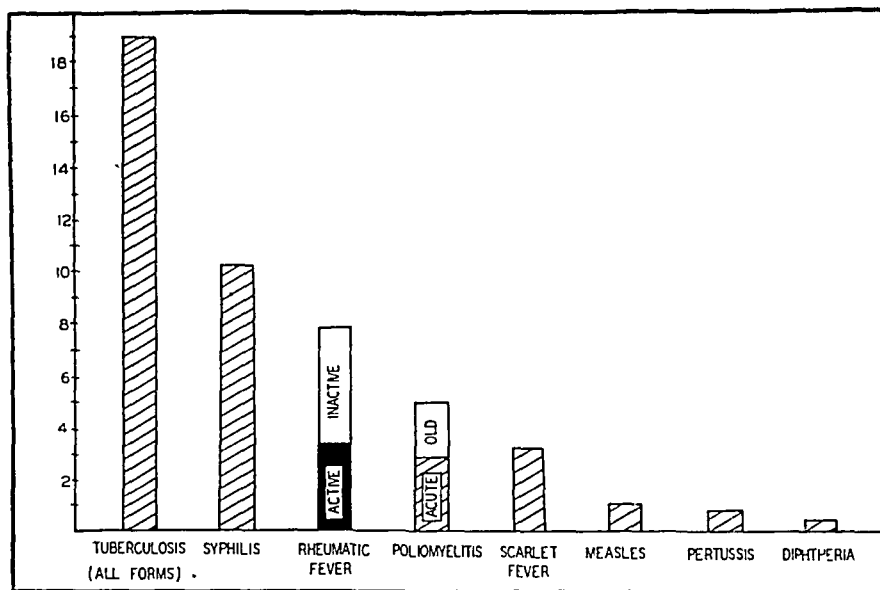


FIG. 5. Comparative rates at which cases representing eight different chronic and acute infectious diseases were admitted to the New Haven Hospital during the period 1929–1938. (From Paul. *Am. J. Pub. Health*, 31:611, 1941.)

still confronted with the fact that this disease contributes a very large proportion of the patients admitted to certain general hospitals. Thus, rheumatic fever stands high in the list of disabling diseases.

Finally, something may be learned of this disease from sample studies on the physical examinations of school children. Such examinations may be indicative of how prevalent juvenile rheumatic heart disease is. Some believe that the diagnosis of rheumatic fever cannot be made by a cursory or a single examination of a child's heart at school. There is much to be said on this side. On the other hand, careful studies of this type seem to show that important data on the prevalence of rheumatic heart disease in childhood can be obtained. In the temperate zone, figures run from 1 to 4 per cent.

Age is a predisposing factor in rheumatic disease. Some years back, Wyckoff in New York City analyzed 1,000 cases of heart disease and classified them according to age. (Fig. 4.) In the childhood age group, that is, between ten and nineteen years of age, he found that eight of every ten

cardiacs had rheumatic heart disease. He also found that, as age increased the relative prevalence of rheumatic heart disease decreased and, at the same time, the relative prevalence of heart disease from other causes increased. This aspect of the disease emphasizes that rheumatic heart disease is a childhood disease or at least begins in childhood. Clinical experience has also corroborated the fact that the greatest incidence of acute rheumatic fever is found among children rather than adults. (Fig. 6.) Many studies have shown that the ages of greatest susceptibility for the onset of this disease are the school age years. First attacks usually occur at about the age of six. High susceptibility is maintained up to puberty and then it rapidly declines. Once the child has had a rheumatic attack, the chances for recurrence are much greater than is the case in one who has not as yet had a first attack. It has further been shown that certain manifestations of rheumatic disease are most prevalent at certain ages. Chorea, for instance, is one of those examples; it is rare to find chorea after twenty-five years of age. (Fig. 7.)

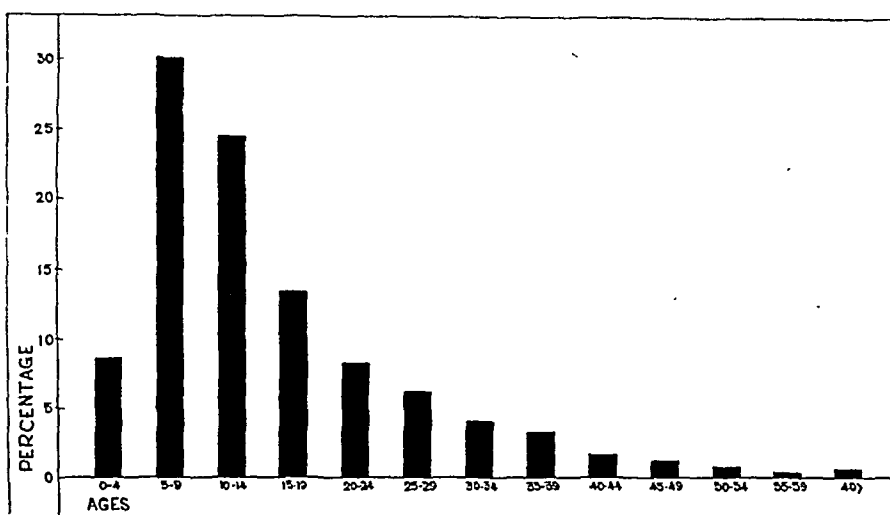


FIG. 6. Percentage distribution by five-year periods of 2,539 first attacks of rheumatic fever with or without rheumatic heart disease, based on past or present histories, among cases admitted to Philadelphia hospitals from January 1, 1930, to December 31, 1934. (From Hedley. *Pub. Health Rep.*, 55: 1647, 1940.)

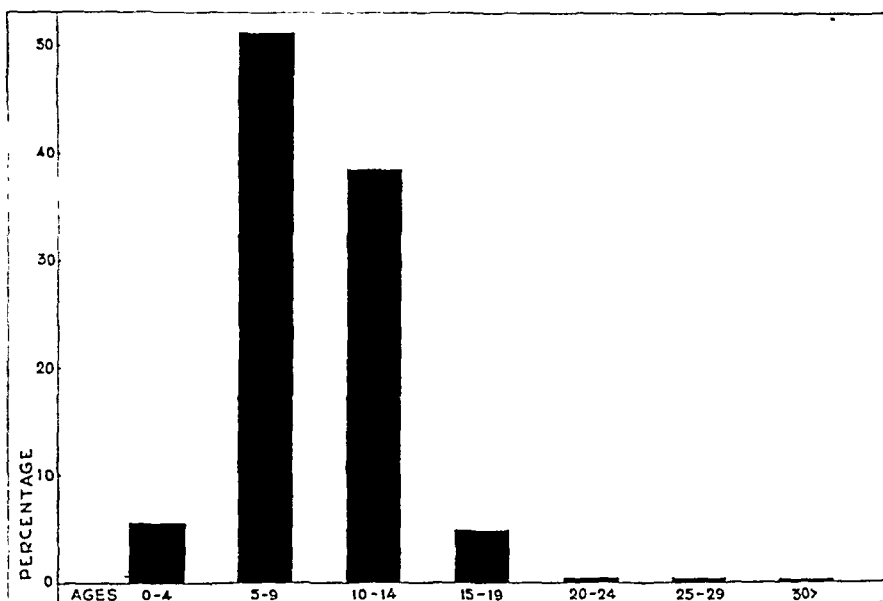


FIG. 7. Percentage distribution by five-year age periods of 920 first attacks of Sydenham's chorea, with or without rheumatic heart disease, based on present or past history, among admissions to Philadelphia hospitals from January 1, 1930, to December 13, 1934. (From Hedley. *Pub. Health Rep.*, 55: 1647, 1940.)

Some idea as to the geographic distribution of rheumatic disease may be obtained from mortality statistics. Studies were made by the Metropolitan Life Insurance Company for the years 1937-1939. (Fig. 8.) In order to avoid the inclusion of other heart disease as much as possible, the Metropolitan Life Insurance Company chose the age group of five to twenty-four. It becomes

obvious from this study that certain areas, for instance, Colorado and Utah, New York, Pennsylvania and Massachusetts, have a much higher mortality rate from rheumatic heart disease than do other areas. It was also evident from this study that the southern states, particularly the Gulf States, have a very low incidence of rheumatic heart disease. This geographical distribution

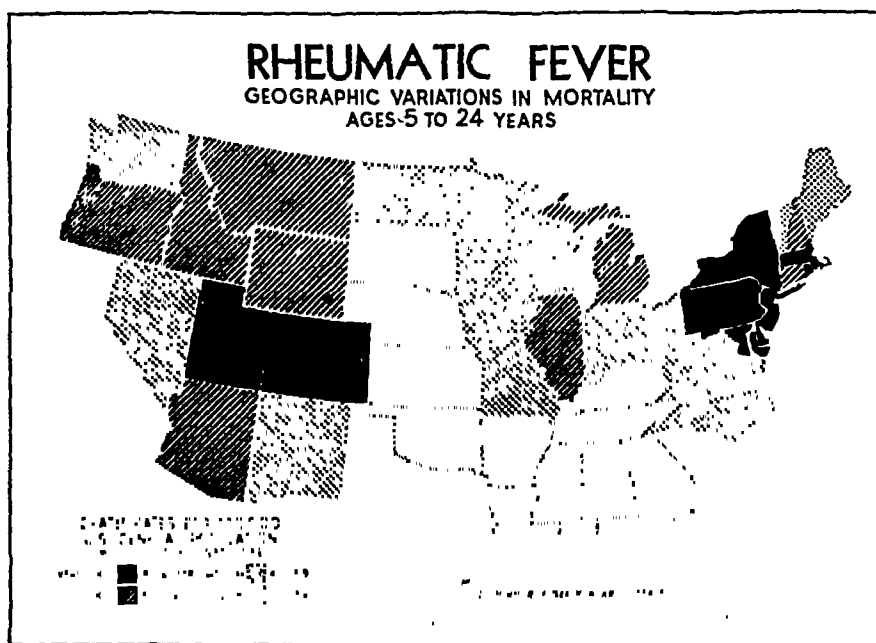


FIG. 8. Map of the United States showing rheumatic fever mortality statistics in the five to twenty-four age group in white persons, for the years 1937-1939, compiled by the Metropolitan Life Insurance Company.

was borne out, in certain instances, by the experience in the Air Forces in the recent war.

Much has been said about the relationship of rheumatic disease to climate. It is incorrect to say that the disease does not occur in warm dry climates but one can say that it certainly is not as prevalent there. We have had occasion to make personal observations on this question in Southern Arizona and in Egypt. New cases appear in such regions but they are not as prevalent as in London or New York City.

In the study of the epidemiology of any disease, racial factors should be discussed. Not much is known about this in rheumatic fever. In New York City and vicinity, two studies indicate that the Irish race seems to lead in the tendency to acquire this disease. Negroes acquire it a little less often than do white people but when they do have the disease, it is apt to be more severe.

Reference has already been made to the fact that much has been learned about the familial character of this disease. One cannot escape the fact that rheumatic fever

runs in families. The hereditary factor appears to be somewhat like that in tuberculosis. On the other hand, we are quite aware that besides hereditary traits, other things "run" in some families, such as *Pediculus capitis* for instance. One can say therefore that those circumstances which concern both the host and his environment, and which favor the spread of contact infection in families, must be considered in evaluating familial prevalence in this disease. Studies by Wilson et al. seem to lead one to believe that rheumatic disease is transmitted along with other hereditary characteristics. I am inclined to subscribe to the concept that the tendency to acquire rheumatic fever is the thing that is inherited rather than the disease process itself.

The environment in which a patient lives is often a factor contributing to the spread of the disease. In Germany, as far back as 1880, rheumatic disease was thought to be a disease of certain districts. Elsewhere it was stated that slum living conditions invite a high incidence of rheumatic disease.

Dr. Hedley has also observed that the

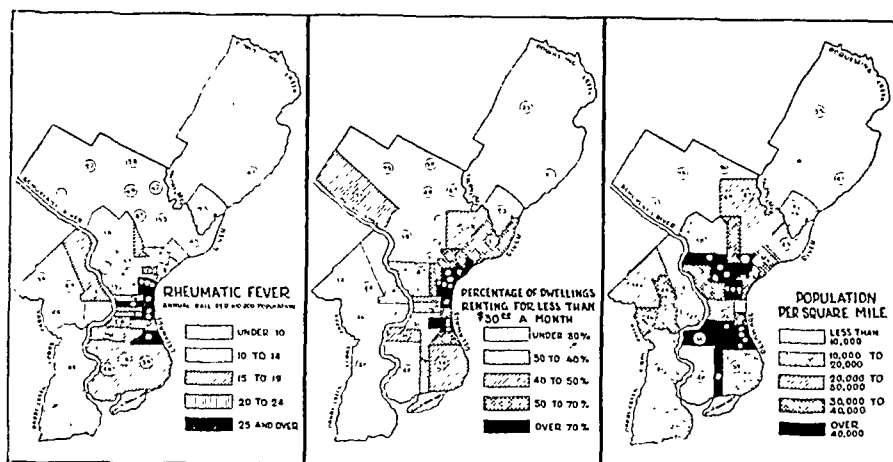


FIG. 9. Maps of the city of Philadelphia, showing, on the left, the distribution by wards of cases of rheumatic fever admitted to Philadelphia hospitals (1930-1934) based on the mean annual number of cases per 100,000 population; in the middle are the low-rental dwellings, and on the right the index of crowding. (From Hedley. *Pub. Health Rep.*, 55: 1845, 1940.)

rate was high in bad urban living conditions in Philadelphia. Some of the criteria for bad living conditions were: crowding, poverty, low rentals, etc. (See Fig. 9.) The same thing was found by workers in Cincinnati, where crowded districts, which were occupied by Negroes at the water front, had a high incidence of rheumatic disease. As in the study of a number of diseases, one can find that crowding predisposes to their spread. Tuberculosis, for instance, is very commonly found in slum districts. While it cannot be said that poverty, per se, is a contributing factor in promoting the spread of rheumatic fever, it can fairly be said that circumstances associated with poverty seem to contribute to the spread of this disease as well as others. Many children in poor homes sleep in the same bed; this is conducive to the spread of disease. Dampness has also been labeled as one of the factors contributing to the spread of rheumatic disease. Poor families are more likely to live in damp houses than are rich families.

In conclusion, one can say that the circumstances under which rheumatic fever occurs are similar to the circumstances under which streptococcal infection occurs. This similarity is due to a common cause.

Methods of determining the prevalence of rheumatic fever have been mentioned and some of the situations in which this disease seems to be most prevalent have been pointed out. It is important to know about these situations and to analyze them because such knowledge may have some bearing on the control of this disease.

#### DISCUSSION

DR. TARAN: The subject of the epidemiology of rheumatic fever is now open for discussion. Are there any questions?

QUESTION: If it is true that rheumatic disease flourishes under certain circumstances which are conducive to other diseases, can one infer that when streptococcal infections occur in conjunction with rheumatic disease that both diseases are the result of a common circumstance and are not related to each other as cause and effect?

DR. PAUL: One cannot infer a common cause because the two diseases exist together but I think the causal relationship between the two diseases is clear from other reasons. It is safe to say that there has never been an epidemic of rheumatic fever without a preceding episode of streptococcal infections. It is true, though, that many strepto-

coccal infections are not followed by, or associated with, rheumatic fever.

QUESTION: What is your opinion about the allergic concept of rheumatic fever?

DR. PAUL: It is an interesting and important theory. It is the theory that both Dr. Swift and the late Dr. Zinsser developed some years back. I believe that the factor of sensitivity to streptococcal products plays an important part in the pathogenesis of this disease. It is a long and complicated subject. Perhaps Dr. Taran can tell us more about the allergic concept.

DR. TARAN: Many years back, the pathologist suspected that the tissue reaction found in rheumatic disease is similar to the tissue reaction found in allergic states. And more recently, the work of Rich and Gregory in Baltimore, seems to show that the tissue reaction in animals in whom anaphylactic shock was produced, was very similar to Aschoff bodies. There is no agreement on this finding.

From the immunologic standpoint, much remains to be learned about the antigen-antibody reaction often found in the blood serum of a patient with acute rheumatic fever. This immunologic response frequently simulates that following a streptococcal infection. That this immunologic response may be responsible for the evolution of a rheumatic attack is not clearly borne out in our experience.

DR. PAUL: For the present, we might say that we have at least two new ways of measuring immunologic reactions in the blood of the rheumatic patient—the anti-streptolysin and the antifibrinolysin titers. Both are also characteristic of type A streptococcal infections. These relatively non-specific antibodies, however, are difficult to measure and the technical difficulties might account for some of the discrepancies found by various investigators. There are probably other antibodies as yet undiscovered. Students in the field believe that few discoveries would be more important

than to find a method for analyzing immunologic reactions in these patients.

QUESTION: Is it not true that the *Streptococcus hemolyticus* is a common organism and is distributed widely among the human race and yet not every one that is infected with the *Streptococcus hemolyticus* comes down with an attack of rheumatic fever?

DR. PAUL: Every one in this part of the world comes in contact with type A streptococci sooner or later. Rheumatic patients, we will say, react in a peculiar manner to the hemolytic streptococcus. I think it is safe to estimate that at least 3 per cent of the young people in our part of the world, when infected with *Streptococcus hemolyticus*, react with a rheumatic response.

QUESTION: What are the criteria for hemolytic streptococcal infections? What do we mean by an epidemic of hemolytic streptococcal infection?

DR. PAUL: The commonest streptococcal infection is probably acute tonsillitis. An epidemic of tonsillitis is sometimes called streptococcal (or septic) sore throat. There are many other forms, including scarlet fever.

In brief, an epidemic of streptococcal infection consists of a group of illnesses caused by type A hemolytic streptococci, and concentrated as to location and time of occurrence.

QUESTION: How often does one find in civilian life a positive streptococcal throat culture?

DR. PAUL: That depends on many circumstances. I believe that it is safe to say that in New York City in the winter time, one out of every four children or young adults might have, at some time or other, a positive throat culture for *streptococcus hemolyticus*. It is important to state at this point, that in recent years, the nose culture has been found to be of greater epidemiological importance than the throat culture. The nasal carrier of type A streptococci is apparently more dangerous than is the throat carrier.



# The Pathology of Rheumatism

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**R**HEUMATIC polyarthritis was known to Hippocrates for he has given a description of arthritis that moved rapidly from joint to joint. The name rheumatism, however, was applied to the disease first by Ballonius<sup>1</sup> in a treatise that was published in 1635, twenty years after his death. Sydenham (1676)<sup>2</sup> gave an exact clinical description and stated that "at times it afflicts this or that joint; at other times the inward parts." He also described the chorea. Boerhaave (1737)<sup>3</sup> mentions that "rheumatism invades sometimes the brain, lungs and bowels." Störck (1762)<sup>4</sup> recognized the pleurisy of rheumatism. Stoll (1788)<sup>5</sup> also spoke of rheumatic pleurisy and rheumatic peripneumonia. Pitcairn (1788)<sup>6</sup> described the pericarditis due to rheumatism. Jenner<sup>7</sup> was well aware of the damage done to the heart by rheumatism.

Our modern literature on rheumatism may be said to begin with the writings of Bouillaud (1837-40).<sup>8</sup> Meynet (1875)<sup>9</sup> described the occurrence of subcutaneous nodules and shortly thereafter a more complete description of these was given by Barlow and Warner (1881).<sup>10</sup> The involvement of the myocardium was described by Besnier 1876, Hardy 1876, West 1878 and Goodhart 1879.<sup>11</sup> Romberg (1894)<sup>12</sup> appears to have been the first to recognize inflammatory lesions in the myocardium. Poynton (1899)<sup>13</sup> described what we now call the submiliary nodule but seemingly did not appreciate its specificity. It was Aschoff (1904)<sup>14</sup> who pointed out the specificity of this submiliary nodule now generally called by his name.

## ASCHOFF OR SUBMILIARY NODULE

The most specific lesion of rheumatic disease is the Aschoff nodule. In the formation of the nodule the initial damage appears to be to collagen that swells and fragments. About these fragments there collect small nononuclear wandering cells, and with them, in some instances a few polymorphonuclear leukocytes. Later appear the more characteristic large cells, the so-called Aschoff cells; these have a faintly basophilic cytoplasm and a large vesicular nucleus with a prominent chromatin mass in the center. Many of these cells have but a single nucleus, others have multiple nuclei. As these larger cells accumulate, the smaller cellular components disappear; finally in the well developed nodules only the larger cells are found. (Fig. 1.)

In preparations of myocardium suitably stained to show the reticulum fibers, the latter are found to be spread apart by the accumulated cells but are not ruptured. As the nodule becomes older, the characteristic cells assume a more spindle shape; they come to resemble more closely connective cells. Collagen is laid down and finally a dense avascular scar remains to indicate the site of the nodule.

There is some dispute as to the nature of the so-called Aschoff cell. Aschoff considered them to be derived from the large mononuclear cells. Letulle, Bezançon and Weil<sup>15</sup> thought they came from heart muscle, but such an origin could not be invoked for those nodules found in other situations than myocardium. In a recent study Clawson<sup>16</sup> concluded they were modified histiocytes.

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Their function is also obscure. Almost always they are in apposition to the fragments of collagen, and their contour on the side adjacent to the collagen conforms to that of the fragment of collagen. Perhaps they may be in the nature of foreign body giant cells, though in only one instance have I seen a fragment of collagen engulfed by an Aschoff cell.

How long an Aschoff nodule may remain unhealed is a matter for conjecture and the question must remain unanswered until the lesion is undeniably reproduced experimentally. Coombs<sup>17</sup> believed them to be of short duration. The submiliary nodule has many points of similarity with the subcutaneous nodule and these persist for a few weeks; so it is probable that the submiliary nodule heals in approximately the same length of time. It is not unusual to find nodules in the myocardium when there has been a long interval since the last attack of arthritis. I have seen typical nodules in the myocardium when the last attack of arthritis was forty-four years before the death of the individual. It would seem more reasonable to assume that the myocardium was being repeatedly damaged than to infer that the nodules had persisted since the last attack of polyarthritis.

Aschoff nodules are widely distributed. In the heart they are found close to the branches of the coronary arteries, especially in the posterior portion of the left ventricle and in the interventricular septum. In these situations they may be very numerous, or it may be necessary to search carefully to find a few of them. They occur in the endocardium, the substance of the valves and the parietal and visceral pericardium. Nodules have been described in the adventitia of the aorta and pulmonary artery (Pappenheimer and Von Glahn,<sup>31</sup> Paul<sup>37</sup>, Meltzer<sup>32</sup>) and in the galea aponeuratica (Tilp,<sup>18</sup> Jacki<sup>19</sup>). Klotz<sup>20</sup> mentions that he has seen them in the subcutaneous tissue, diaphragm, pulmo-

nary artery and aorta. I have seen them in peri-esophageal tissue and near an intercostal artery and also in the diaphragm. (For more complete discussion concerning the Aschoff nodule the reader is referred to the review of Clawson.<sup>21</sup>)

Rarely, widespread necrosis of the myocardium occurs with the Aschoff cells scattered throughout the necrotic area. Such a lesion was found in the heart of a child three years of age, together with dense avascular scars of corresponding size.

#### RHEUMATIC ENDOCARDITIS

The characteristic recent vegetation is a small wart-like mass having a dull yellow color and roughened surface. These verrucae often extend as a chain along the line of closure of the tricuspid, mitral and aortic leaflets; they are less frequently found on the pulmonic cusps. Sometimes flatter, broader, less wart-like vegetations are seen on the mitral valve. The vegetation in the early stage is composed of a granular material that is believed by many to be fibrin. I have not been able to demonstrate fibrin except at the surface where the vegetation is in contact with blood and at the base where it joins the underlying tissue. As the vegetation becomes older the material of which it is composed is more compact. In the earliest stage the vegetation is tough and does not break away readily, hence infarcts in distant organs are not seen in uncomplicated rheumatic cardiac disease. (Fig. 2.)

Healing of the vegetation takes place by the ingrowth of connective tissue from the valve. It is not unusual to find dense bits of the vegetation buried in the connective tissue with more recent and less dense granular material on the surface. Endothelium grows over the surface as healing progresses. Finally the vegetation is completely replaced by connective tissue and covered by endothelium; it is then grey, smooth and translucent.

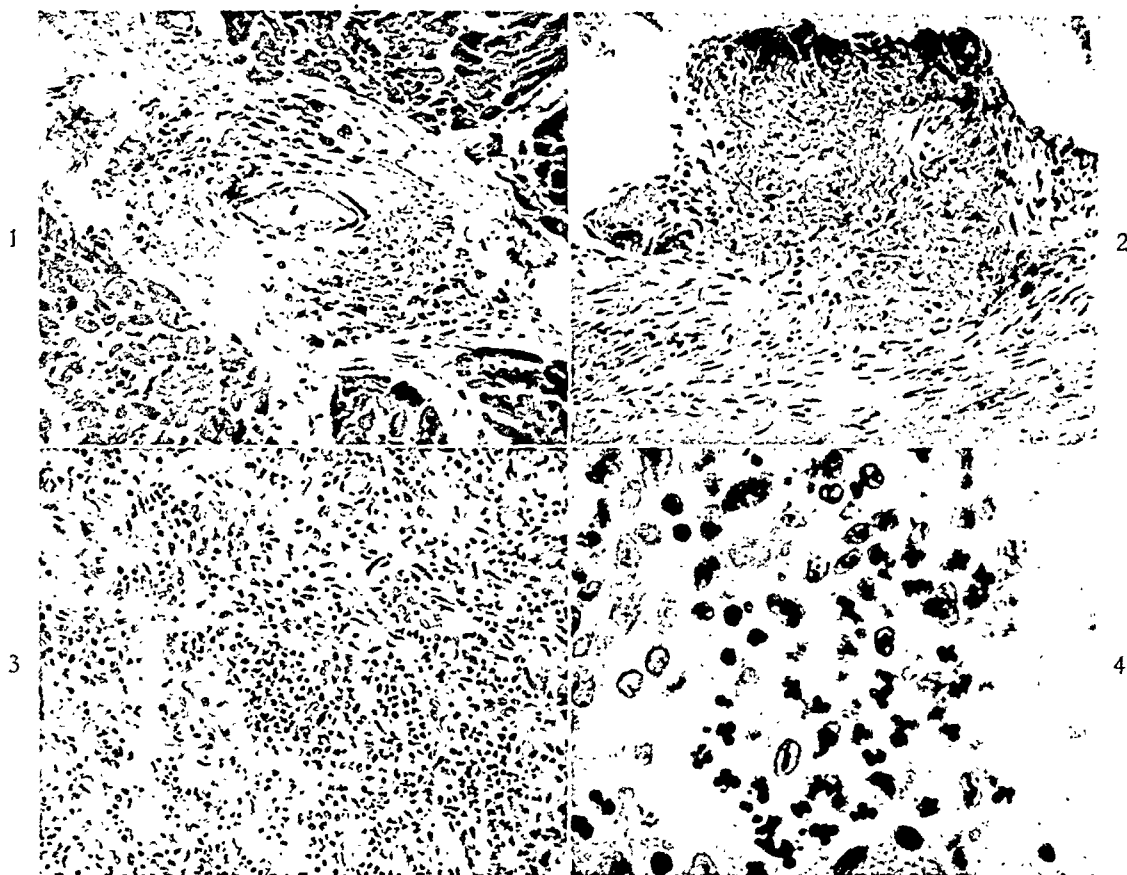


FIG. 1. Acute rheumatic myocarditis; Aschoff bodies.

FIG. 2. Rheumatic verruca; mitral valve.

FIG. 3. Acute rheumatic interstitial valvulitis; mitral valve (low power).

FIG. 4. Acute rheumatic interstitial valvulitis; mitral valve. High power magnification of central portion of Figure 3.

Other and more important changes occur within the valve leaflet; these have been emphasized by Coombs,<sup>53</sup> Swift,<sup>22</sup> and Kugel and Epstein.<sup>38</sup> Aschoff nodules are infrequently found within the valve. More often there is a diffuse inflammation characterized by polymorphonuclear leukocytes, eosinophils and large and small mononuclear cells. (Figs. 3 and 4.) When the endothelium is damaged the vegetation forms. Following the acute interstitial valvulitis there is an increase of connective tissue within the leaflet and blood vessels penetrate into the base of the valve.

Undoubtedly this acute interstitial valvulitis is repeated and increase of connective tissue follows each attack. It is not the healing of the vegetation but this scarring of the

valve that is responsible for the thickening, fusion and retraction of the leaflets. Calcium is often deposited in the damaged leaflets and renders them still more inflexible. Similar inflammation and subsequent scarring take place in the chordae tendineae and cause them to shorten, thicken and fuse together. In some instances the chordae are so shortened that the tip of the papillary muscle is brought close to the edge of the leaflet.

In the auricular endocardium a now well recognized form of endocarditis may be found. The surface of the left auricular endocardium is thrown up into irregular ridges and folds, most often above the posterior leaflet of the mitral valve; similar irregularities may be continued across the

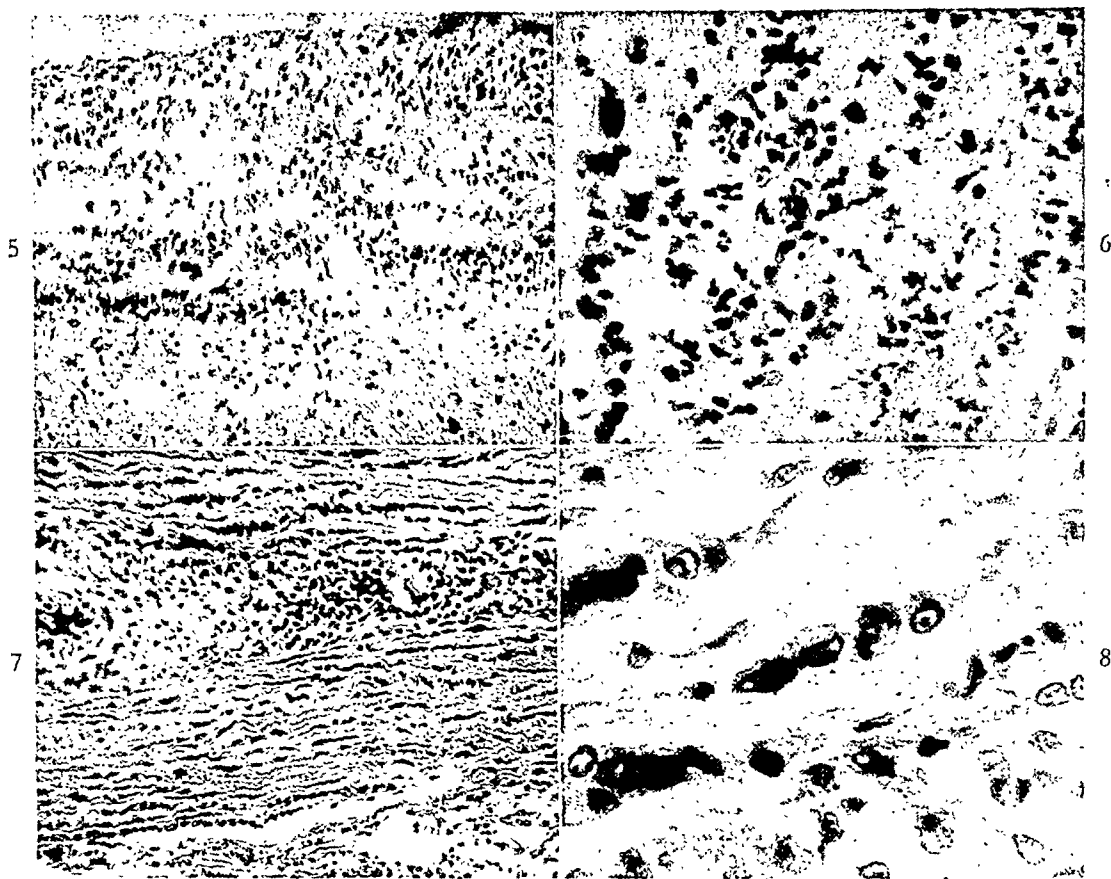


FIG. 5. Rheumatic endocarditis; left auricle; palisade of large cells about altered collagen.

FIG. 6. Rheumatic endocarditis; left auricle; acute reaction; many cells having distorted nuclei.

FIG. 7. Rheumatic aortitis; large cells held in rows by elastic fibers of media; acute reaction about penetrating vessel.

FIG. 8. Rheumatic aortitis. High power magnification of field in Figure 7; large cells held in rows by elastic fibers.

auricular surface of the leaflet to the line of closure. In other parts of the auricular endocardium rounded or oval elevated plaques may be found. In the acute stage, the involved endocardium is tawny yellow and dull, in the later stage grey and glistening. Calcium is at times deposited in these lesions.

As elsewhere, the initial stage is swelling of the collagen. Large cells collect about the bands of altered collagen in a palisade fashion. (Fig. 5.) Occasionally an Aschoff nodule is found but usually the elastic fibers hold the cells in rows. With these large cells are neutrophilic and eosinophilic leukocytes and small mononuclear cells.

Also other and equally characteristic cell

accumulations are described. These consist of polymorphonuclear leukocytes, small mononuclear cells and large cells differing from the typical Aschoff cell. These large cells are pale staining and the vesicular nucleus has a delicate membrane; the cytoplasm is not basophilic and the nucleolus is small. Always the long axis of the cell is perpendicular to the endocardial surface. Many distorted, elongate and bizarre nuclei are found in these accumulations; they are in part the nuclei of deformed polymorphonuclear leukocytes, others belong to the large mononuclear cells. (Fig. 6.) The cell collections frequently lie in the inner part of the endocardium. When the endothelium is damaged a vegetation forms.

The elastic fibers are spread apart, stretched, fragmented or ruptured by the cell accumulations. In healing an avascular connective tissue springs up that is directed perpendicularly to the surface and penetrates into any vegetation present. Delicate elastic fibrils are later found in this connective tissue and follow its direction. Calcium may be deposited in the later stages.

The outer portium of the endocardium is edematous; fibrin and polymorphonuclear neutrophiles and eosinophiles are found here. Healing takes place by an ingrowth of granulation tissue from the adjacent myocardium that penetrates for a short distance into the endocardium (Claude and Levaditi,<sup>23</sup> Harper,<sup>24</sup> Hertel,<sup>25</sup> Stewart and Branch,<sup>26</sup> MacCallum,<sup>27</sup> Von Glahn<sup>28</sup>).

In a series of eighty-seven hearts Gross<sup>29</sup> found histologic evidence of auricular endocardial damage in each heart.

#### PERICARDITIS

The characteristic fibrinous exudate may cover the entire surface of the heart or be restricted to a small area at the base. The parietal pericardium is correspondingly involved. With the fibrin there may be a very small quantity or a large amount of fluid. Granulation tissue grows into the exudate from the myocardium and parietal pericardium and may lead to obliteration of the pericardial space with permanent union between the heart and parietal pericardium.

#### RHEUMATIC DISEASE OF BLOOD VESSELS

Numerous observers<sup>30-36</sup> have given description of the damage done to the aorta in rheumatism. Nodular Aschoff bodies are found in the adventitia or scattered Aschoff cells are observed at the junction of adventitia and media. Large cells held in rows by the elastic fibers are found in the media and along the course of the vasa vasorum. With these large cells are frequently seen

polymorphonuclear leukocytes. (Figs. 7 and 8.) The elastic fibers are fragmented in the immediate neighborhood, but the fragmentation is not so extensive as that seen in syphilitic aortitis. Dense avascular scars surround the nutrient vessels when the lesion heals.

Pappenheimer and Von Glahn,<sup>31</sup> and Perla and Deutsch<sup>35</sup> have described a gross lesion in the aorta that is distinctive. Elevated, brownish, almost transparent intimal plaques or ridges are found closely resembling the lesion of auricular endocarditis and easily separated from arteriosclerosis and syphilitic aortitis.

The histologic alterations are swelling of the fibrillar material of the intima with surrounding large cells having basophilic cytoplasm and large, vesicular nuclei with a prominent chromatin mass. Fibrin may be present on the surface. The elastic fibers are disrupted and scarring extends into the adjacent media. In other places a more diffuse inflammatory reaction occurs, polymorphonuclear leukocytes and cells with elongate nuclei being found in the intima quite similar to the lesion in the left auricle. (Fig. 9.) These changes cannot be attributed to extension of the inflammation from the aortic valve cusps as they are too far removed from them and must be considered independent lesions.

Lesions in the pulmonary artery similar to those in the aorta have been described by Paul,<sup>37</sup> Kugel and Epstein<sup>38</sup> and Gray and Aitken.<sup>36</sup>

In the smaller vessels numerous observers mention swelling and proliferation of the endothelium. A specific type of involvement of arterioles and capillaries has been described. There is a fibrinous exudate beneath the endothelium, at times extending through the vessel wall and often associated with hemorrhage. The vessel wall is necrotic and about the vessel collect polymorphonuclear neutrophiles and eosinophiles, large mono-

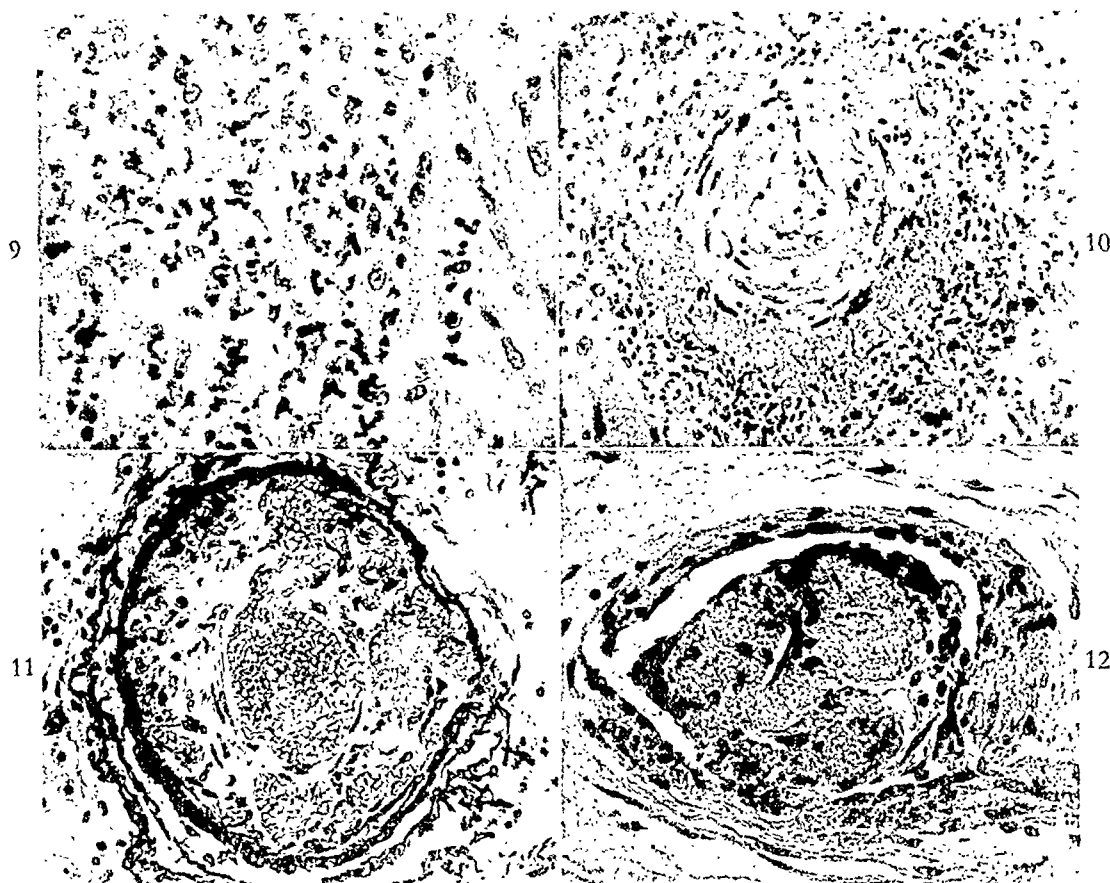


FIG. 9. Rheumatic aortitis; acute reaction similar to that seen in left auricle; polymorphonuclear leukocytes and cells with distorted nuclei.

FIG. 10. Lung: rheumatic arteritis; necrosis of vessel wall with acute inflammatory reaction.

FIG. 11. Lung: rheumatic arteritis; healed lesion with formation of new channels; elastic tissue—hematoxylin and eosin stain.

FIG. 12. Verrucous arteritis; heart.

nuclear cells and cells with distorted nuclei, similar to those seen in the auricular endocarditis. The elastica is stretched, fragmented or ruptured. Thrombi are not found. (Fig. 10.) The surrounding capillaries are greatly engorged. Healing takes place in one of two ways. When only fibrin is found, it is replaced by connective tissue and the end result simulates an obliterating endarteritis.

If hemorrhage is present with the fibrin, endothelial cells creep down and surround the extravasated blood forming new capillaries that empty into the narrowed lumen. In the affected artery, one of the new capillaries may begin in the media and penetrate through a gap in the elastica interna to communicate with the lumen; in

other instances one of the new capillaries situated close to the internal elastic membrane may sweep half way around the vessel before it empties into the lumen. (Fig. 11.) The healed lesion, when there has been hemorrhage with the fibrin, closely resembles an organized and canalized thrombus, though careful study will disclose the absence of any remnant of a thrombus and no hemosiderin is to be seen. I have not observed any aneurysm formation as is so frequently found in periarteritis nodosa.

These lesions have been described in the smaller branches of the pulmonary, renal and pancreatic arteries, in the ovary and about the adrenals (Von Glahn and Pappenheimer).<sup>39</sup>

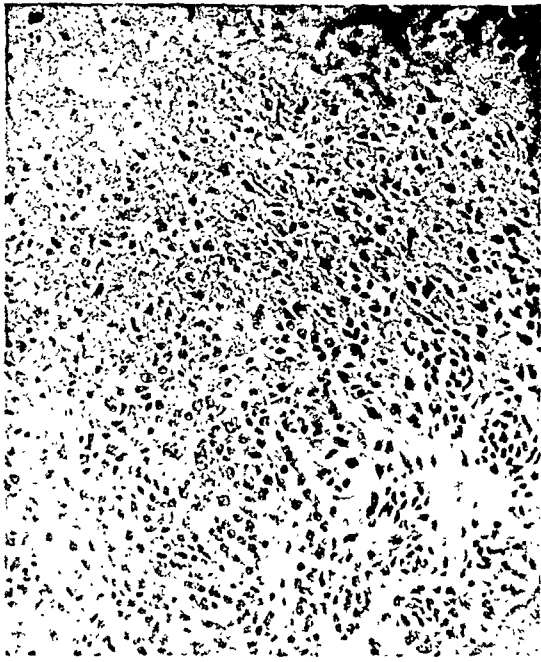


FIG. 13. Rheumatic subcutaneous nodule. A small portion of the center is shown with surrounding cellular reaction and new capillaries.

There are also lesions of the larger arteries such as the celiac axis and hepatic artery. Translucent intimal plaques are found consisting of fibrillar material infiltrated with leukocytes and large cellular components with distorted nuclei. Leukocytic infiltrations are present in the media and adventitia.<sup>39</sup> Holsti,<sup>40</sup> in a series of cases designated as arthro-nephro-cardiopathies, and also in a discussion of changes in the tonsils of a rheumatic patient, describes a verrucous arteritis. The process is apparently one of thrombosis with organization resulting in nodular or finger-like projections from the wall into the lumen. (Fig. 12.)

#### LUNGS

Frequent mention has been made of rheumatic pneumonia, chiefly in clinical reports. Recently descriptions have been given of a specific lung lesion (Paul,<sup>41</sup> Naish,<sup>42</sup> Fraser,<sup>43</sup> Eiman and Gouley,<sup>44</sup> Gouley,<sup>45</sup> and Neuberger, Geever and Rutledge<sup>46</sup>).

The lungs are involved to varying degrees

and the gross appearance would seem to be very characteristic, as it is quite different from that of the usual types of pneumonia.

The affected portions are firm but elastic and on section the surface of such areas is smooth and deep red. The alveolar septa are infiltrated with large cells, often multinucleated, with plasma cells, lymphocytes and some polymorphonuclear leukocytes. Nodular accumulations of large cells, that resemble Aschoff nodules, are described in the interlobular septa.

The alveoli may contain a little serum with fibrin, or blood and a few neutrophils. The alveolar lining cells are desquamating. The blood vessels are engorged. There is also described fibrinoid necrosis of the alveolar septa. The exudate in the alveoli may undergo organization with the formation of fibrous plugs. In the late stage the septa are widened by fibrous tissue and the alveolar lining cells prominent. Some of these cases have associated lesions of the arteries as outlined above.

A fibrinous pleurisy is of fairly frequent occurrence even in the absence of rheumatic pneumonia.

#### SUBCUTANEOUS NODULE

The subcutaneous nodule is found where bony prominences are close to the skin. The center of the nodule is composed of what appears to be swollen fragmented collagen. About this is a zone of somewhat spindle-shaped cells; at the periphery are large mononuclear cells and dilated capillaries with prominent endothelial cells.<sup>10,18,19</sup> (Fig. 13.)

Massell, Mote and Jones<sup>47</sup> have reproduced these nodules by injecting blood from the patient into the subcutaneous tissue about the elbow. For several days the area of injection was rubbed at intervals and a nodule resulted. In a few instances nodules formed following the injection of salt solution and rubbing of the area.

These induced nodules were in every way identical with the spontaneous nodules.

#### RHEUMATIC PERITONITIS

That the peritoneum may be involved in rheumatism has been clearly established. Localized portions appear yellowish and edematous. In addition to edema, there is an infiltration of large mononuclear cells, plasma cells and a few leukocytes. Sometimes fibrin is on the surface' (Paul,<sup>48</sup> Wood and Eliason<sup>49</sup> and Rhea<sup>50</sup>).

#### RHEUMATIC NEPHRITIS

Blaisdell<sup>51</sup> has described changes in the kidney attributed to rheumatism. The lesion is interstitial and the glomeruli are not damaged. There are nodular collections of lymphocytes, plasma cells, a few polymorphonuclear leukocytes and indefinitely outlined cells with pale nuclei in the adventitia of the vessels. Occasionally the same types of cells are found in the media of the arterioles with degeneration of the muscle. The intima is not constantly nor characteristically involved.

#### JOINTS

The joint cavity contains an excess of fluid in which is a little fibrin and a few polymorphonuclear leukocytes. There is edema and hyperemia of the synovial membrane with edema of the periarticular tissues. Focal necroses in the capsule, thrombosis of the smaller arteries and cellular accumulations comparable to those of the subcutaneous and Aschoff nodules are found in the periarticular tissues (Fahr,<sup>52</sup> Coombs,<sup>53</sup> Swift<sup>54</sup>).

#### CHOREA

The brain shows little but hyperemia grossly. The histologic lesions though widely scattered are localized especially in the gray

matter, the basal ganglia, brain stem and in the neighborhood of the aqueduct. There are thrombi in the smaller arteries, hemorrhages, engorgement of the vessels and proliferation of the endothelium with fat droplets in some of these cells. Perivascular and diffuse infiltrations of wandering cells, chiefly mononuclear are found; areas of softening sometimes occur. The ganglion and cortical cells show varying degenerative changes (Poynton and Holmes,<sup>55</sup> Greenfield and Wolfsohn,<sup>56</sup> Urechia and Mihalescu<sup>57</sup> and Castrén<sup>58</sup>).

Von Sántha<sup>59</sup> has described thrombi in the pial veins and arteries with canalization, intimal thickening and subendothelial exudate in these vessels. In the brain there is an acute endarteritis with an increase of endothelial and adventitial cells and sometimes fibrin in the vessel wall, extending out into the surrounding tissue. These vessel changes lead to focal necrosis in all parts of the cerebrum but especially in the cortex.

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# Conference on Therapy

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## Treatment of Rheumatic Fever

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy* by The Macmillan Company.

DR. HARRY GOLD: The treatment of rheumatic fever is the subject of our conference this afternoon. Dr. Robert Watson of the Rockefeller Institute will make the opening remarks.

DR. ROBERT WATSON: Rheumatic fever is a febrile disease of unknown etiology. It is an essentially chronic disease with a high tendency to recurrences, often presenting acute phases. Its clinical manifestations are numerous and varied, the chief ones being arthritis, carditis and fever.

There is no specific cure for rheumatic fever, although dramatic effects on some of the signs and symptoms of the acute phase of the disease are produced by salicylates, aminopyrine, and cinchophen or neocinchophen.

The patient who presents himself with the acute manifestations of rheumatic fever is put at rest in bed. He is given a well balanced and nourishing diet. Nursing care can be of considerable comfort to the patient at this time, particularly if he has acutely inflamed joints.

Of the antirheumatic drugs, one of the derivatives of salicylic acid is most commonly employed, either acetylsalicylic acid (aspirin), or sodium salicylate. There seems to be no essential difference between the therapeutic effects of the two. I usually give from 5 to 10 Gm. per day, the total dose being divided into six fractions, adminis-

tered at four-hour intervals during the day and night. Sodium bicarbonate is given simultaneously in doses one-half of that of the salicylates. The object is to give enough salicylate completely to relieve the acute symptoms, including the joint manifestations and the fever, whenever possible. The tolerance and the requirements differ from one individual to another. A plan commonly recommended in many of the modern textbooks is to give salicylates at frequent intervals at the beginning to the point of toxicity and then, after a brief interval of interruption, to resume the drug at a lower dosage level. I see no value in the initial dosage to the point of toxicity. Doses between 5 and 10 Gm. daily usually produce the desired effects, without inducing toxic symptoms.

The drug is best tolerated after meals, and if the time for a dose happens to fall between meals, a glass of milk and crackers taken before the drug often controls much of the epigastric burning and discomfort. There seems to be a tendency for patients to develop a tolerance to the local gastric effects; they often complain of anorexia, tinnitus, nausea and occasionally vomit, during the first three or four days, but then these symptoms seem to disappear and the drug is then taken without difficulty. If nausea, vomiting, deafness or tachypnea persist, it is usually an indication of salicylism, indicating that the limit of systemic

tolerance has been exceeded. In that case the dose may be decreased, or the amount of sodium bicarbonate increased. Within limits, either of these procedures has the same effect, namely, to reduce the concentration of salicylate in the blood, since the occurrence of salicylism is related to the blood level of the drug. In those in whom vomiting occurs from other causes, the drug may be administered by rectum. Sodium salicylate is usually given in doses of 3 to 4 Gm. dissolved in 150 to 200 cc. of warm starch water three to four times a day.

For patients who cannot tolerate adequate doses of salicylates, aminopyrine may be given, although it is unwise to use it routinely because of its tendency to produce granulocytopenia. Aminopyrine is as effective as the salicylates in about one-half of the dosage of the latter. It may be given in doses of 2 to 5 Gm. daily, divided into six equal fractions, and administered in the same way as the salicylates. It causes no gastric irritation and does not produce signs or symptoms of salicylism. It is not necessary to use sodium bicarbonate with it. When the patient is taking aminopyrine, it is necessary to check the blood frequently and discontinue the drug at the first signs of leucopenia or a decrease in the granulocytes.

Cinchophen and neocinchophen are also effective in rheumatic fever, and are sometimes used in place of the salicylates. They are apparently equally as effective in doses similar to those of the salicylates, but I do not recommend them because of the danger of liver damage. I mention them only because they have been employed, and to indicate that other drugs not related chemically to salicylates are effective.

On a regimen which includes bed rest and adequate doses of salicylates, the response of most patients in the acute phase of rheumatic fever is usually dramatic; the temperature falls to a normal level within twenty-four to forty-eight hours; the joint

pains subside promptly; fluid which may be present in the joints disappears within a few days; the appetite improves; the patient begins to gain weight; the systemic symptoms disappear; and the leukocytosis gradually subsides within the first week or two. The decline of the elevated sedimentation rate tends to lag, but after a week or two begins to fall toward a normal level. The sedimentation rate is probably the best single test for following the course of the disease. I usually continue salicylates for a period of two weeks after the patient is not only asymptomatic, but the leukocytosis, the elevated sedimentation rate, the fever and the electrocardiographic abnormalities have all disappeared. The dosage is then gradually reduced over a period of a week to ten days, when it is discontinued if the patient's condition remains unchanged. In the event that there is no sign of recurrence after the patient is without the drug for two weeks, he is allowed up, and the length of time he is up is gradually increased, provided the patient shows no signs of active infection. The period of convalescence and the degree of physical activity allowed, depend on the amount of cardiac damage the patient has suffered.

In a small percentage of cases, following the withdrawal of salicylates, an elevation in the sedimentation rate may occur without any other signs or symptoms of "activity," but this usually will return to normal in a very short time. In still another group all the signs and symptoms of "activity" may return, and in this event the patient is put back at bed rest and on salicylates.

DR. GOLD: A very dramatic picture has recently been painted of the effect of salicylates in acute rheumatic fever: here is a patient very ill, with high fever, and acutely painful and swollen joints; he receives 10 or 20 Gm. of sodium salicylate intravenously; in five hours he is virtually free of symptoms; in twenty-four hours he is afebrile; and in

two weeks the sedimentation time is back to normal; he does not develop heart disease. This is the kind of picture we see from Coburn's recent publications. Is there anyone here who has had similar experience?

DR. MAY G. WILSON: That is not the way the matter looks in children. I know of several studies in which the administration of large doses of salicylates intravenously made the patients feel better but the disease continued to progress.

DR. SAMUEL Z. LEVINE: The fall of the sedimentation time, like the prolongation of the prothrombin time, may have nothing to do with the cure of the disease, and is simply one of the effects of the salicylates, not specific for rheumatic fever.

DR. WATSON: At this point it might be well to say a word about the so-called "massive" dose method of the use of salicylates in the treatment of rheumatic fever. This brings up an old controversy, one that dates back to the beginning of the present century. Coburn revived this question in 1943. He believed that by means of "massive" doses, 10 Gm. daily or more, the cardiac sequelae could be prevented. The system he recommended involved the use of from 10 to 20 Gm. of sodium salicylate intravenously in 1,000 to 2,000 cc. of physiological saline daily for a period of about seven days. This was followed by a period of about three weeks in which the patient received 10 Gm. daily by mouth, administered in fractions of 1.5 Gm. and about half as much sodium bicarbonate every four hours day and night. These doses were sufficient to produce salicylate blood levels of about 35 mg. per 100 cc. of plasma. The plan was to maintain patients on this regimen until symptoms and signs of "activity" subsided, and the sedimentation time returned to normal. The treatment was resumed in the event acute symptoms and signs recurred after withdrawing salicylates. Coburn's statistics are very striking, but

attempts by other workers to repeat his results have not been successful. We are back to where we were many years ago, with no proof that "massive" doses of salicylates accomplish anything more than those necessary to control the signs and symptoms. Furthermore, there seems to be no justification for the routine use of intravenous therapy. There is danger of severe toxic effects after the intravenous administration of large doses of sodium salicylate. Moreover, the blood level necessary for therapeutic results is reached sufficiently rapidly by oral doses.

DR. JANET TRAVELL: Can you not attain the same blood levels of salicylates by the oral route as by intravenous injection?

DR. GOLD: Yes, you can, but it takes longer to get there. The large intravenous injections may attain a maximum blood level in a few hours, while the usual system of oral doses attain such levels only after about twenty-four hours or longer. There is the other point that if one attempts to reach maximum levels too quickly by the oral route through the use of larger doses, vomiting results and the drug is lost. In vomiting resulting from the intravenous administration, there is no chance of losing the drug.

DR. TRAVELL: Dr. Lewis A. Conner used to order the salicylates routinely to be given by rectum.

DR. WILSON: I have used it that way and it is very satisfactory.

DR. WATSON: The patient with rheumatic polyarthrititis and carditis, who develops cardiac failure, is treated in the same manner as others, in addition to the usual measures for the treatment of heart failure, namely, elevation of the head of the bed, limited fluids, restricted salt intake, digitalization and diuretics if needed. There is the belief that digitalis is contraindicated in acute rheumatic carditis. I do not share that view, and it is my experience that the drug is often beneficial. There is the fact that in

active rheumatic carditis, digitalis does not produce effects as dramatic as in cases of heart failure due to other causes, such as in cases of hypertension or inactive rheumatic heart disease. It also should be given more cautiously, since some patients with acute rheumatic carditis do not tolerate the drug very well. The xanthine diuretics are useful in some patients with heart failure due to active carditis. I have used theobromine-calcium salicylate in doses of 3 to 4 Gm. with favorable results. The mercurial diuretics are also beneficial in some of these cases, as they are in other forms of heart failure.

Thus far, I have considered chiefly those cases who respond satisfactorily, those in whom the signs and symptoms of the disease subside in a matter of a few weeks or months of treatment. There are many patients who do not respond so satisfactorily to treatment; the sedimentation rate remains elevated; the electrocardiographic changes persist; and other signs and symptoms of the disease continue on for a period of months. In these it is well to continue the salicylates. Physical activity should be restricted, although it is often not possible or necessary to keep the patient at bed rest for long periods of time such as eight to twelve months or more. Bathroom privileges and sitting in a chair do not seem to do them any harm. In these cases the treatment has to be suited to the individual case.

A word or two about some of the other drugs. Codeine and morphine are not very useful for the relief of the joint symptoms. They have to be given in such large doses as to cause drowsiness and depression in order to provide relief. Codeine is sometimes effective in controlling the precordial pain in some cases. The dangers of morphine in patients with heart failure are well known.

Sulfadiazine is effective in preventing recurrences when given continuously during the inactive phase of the disease. It is not

effective during the active phase of the disease and there is experience indicating that the sulfonamides administered during the active phase, may cause exacerbation of signs and symptoms.

Penicillin is likewise ineffective in rheumatic fever. In our experience its use has no effect on the course of the disease.

As far as I know, streptomycin has not been tried. I see no reason why it should be effective, but, no doubt, it will be tried when more of it becomes available.

The question of a pericardial tap frequently arises in patients with acute rheumatic fever. To differentiate pericarditis with effusion and tamponade from a greatly dilated heart is often a difficult problem. The two are easily confused, and oftentimes, pericardial taps yield only cardiac blood. Adequate doses of salicylates given early will often prevent the development of pericardial effusion sufficient to give rise to cardiac tamponade.

Pleuritis is another very common manifestation of active rheumatic fever. It is treated as is pleuritis in any other disease, in addition to salicylate therapy. Occasionally, thoracentesis is necessary, particularly in those cases with advanced failure.

Epistaxis sometimes becomes a serious problem in rheumatic fever. Those who are prone to develop it are instructed to use a little vaseline or 1 or 2 drops of mineral oil in the nose twice a day. This simple measure often eliminates further trouble from this source. The question recently has been raised as to whether the epistaxes are due to a prolonged prothrombin time as a result of the administration of salicylates, since it has been shown that salicylates in the doses used in rheumatic fever may cause some prolongation of the prothrombin time, and in toxic doses may prolong the prothrombin time very greatly. In our own experience with a small series of patients, the prothrombin time was found to be

slightly prolonged during active rheumatic fever before salicylates were given, and changes in the prothrombin time followed more closely the course of the active rheumatic fever than the dosage of salicylates. There also is the question of whether vitamin K should be used routinely with salicylates in rheumatic fever. I do not employ it routinely, but I do use it in those patients who develop epistaxis or other hemorrhagic manifestations.

Thus far, we have said nothing about climatotherapy, the matter of moving patients to other climates for prophylaxis or treatment. I shall be glad to answer any questions that may arise in this regard during the discussion.

Finally, there is the problem of foci of infection, such as the tonsils and the teeth. I believe it is usually best to wait until the active disease has subsided before undertaking surgical measures for the removal of possible foci. The indications for these measures are the same as in an otherwise healthy individual, and not with the idea that it will influence the course of the rheumatic fever favorably. There is another point, that when we remove the tonsils or teeth from a patient who has had rheumatic fever, it is wise to give large doses of penicillin in an effort to prevent subacute bacterial endocarditis which sometimes develops in these patients after these procedures. This drug should be started a short time before the operation and continued for about forty-eight hours after.

DR. GOLD: The subject is now open for your discussion. Are there any questions?

DR. McKEEN CATTELL: I wonder if you or Dr. Watson would enlarge on the mechanism of action of the sodium bicarbonate in reducing the blood levels of salicylates.

DR. GOLD: Dr. Watson, would you care to answer that?

DR. WATSON: It is probably due to increased renal excretion caused by the bi-

carbonate. There are several recent papers all published in 1946 showing that sodium bicarbonate increases urinary excretion of salicylate, namely, the one by Caravati and Cosgrove in the *Annals of Internal Medicine*, and those by Smith et al., and Lester et al., in the *Journal of Pharmacology*.

DR. CATTELL: Is the routine use of bicarbonate with salicylate for the purpose of reducing the blood level or for reducing gastric irritation?

DR. WATSON: The chief purpose is to reduce gastric irritation. It certainly relieves the epigastric burning which is apt to occur immediately after the salicylates. However, only by lowering the blood level can one control the signs and symptoms of true salicylism.

DR. CATTELL: It would seem that one really defeats one's purpose to the extent that the bicarbonate reduces the blood level of salicylate, is it not so?

DR. WATSON: That is right. However, by proper adjustment of the doses of the two drugs, one can get an effective blood level and still do away with the gastric irritation.

DR. GOLD: There is considerable controversy in the literature concerning the effect of sodium bicarbonate on the excretion of salicylates. In the well known textbook on Pharmacology by Goodman and Gilman, the statement is made that sodium bicarbonate does not hasten salicylate excretion. In relation to the blood level, there is the point made by Bradley et al. in 1936 that sodium bicarbonate slows up gastric absorption because of the rise in the pH of the solution in the stomach. The recent paper in the *Journal of the American Medical Association* by Smull, Wégria and Leland mentions two possible causes for the fall of the blood level, aside from excretion, interference with the absorption of salicylate from the intestine and increase in the extracellular fluid by the bicarbonate which leads to a decrease

in the concentration of the salicylate in the blood.

Again, as Dr. Cattell pointed out, the sodium bicarbonate tends to defeat the purpose of large doses. One might just as well give smaller doses than larger ones counteracted by sodium bicarbonate which reduces the blood level of salicylate.

DR. WALTER MODELL: Did Dr. Watson state that if adequate doses of salicylates were given, pericarditis with effusion was not likely to occur?

DR. WATSON: Yes, if the drug is started early enough.

DR. MODELL: Would this not indicate that salicylates have a specific action in preventing cardiac complications?

DR. WATSON: No. Salicylates do not seem to affect the proliferative reaction of the disease and it is this that probably causes most of the valvular damage. It is the exudative reaction which is to a large extent controlled by the salicylates.

VISITOR: Is the response of the temperature to salicylates in rheumatic fever sufficiently characteristic to use this as a means of differentiating rheumatic fever from other fevers in the absence of the characteristic joints?

DR. WATSON: The temperature response to salicylates in rheumatic fever is usually much more striking than in other types of infectious diseases, particularly in those diseases with joint manifestations such as rheumatoid arthritis, lupus erythematosus, etc.

DR. GOLD: Would it enable one to distinguish an attack of rheumatoid arthritis from one of rheumatic fever?

DR. WATSON: It would help.

DR. CATTELL: It was not clear to me how long Dr. Watson would continue the salicylates after the acute phase of the disease had subsided. Suppose the sedimentation remains elevated for six months, at what point would one discontinue the drug?

DR. WATSON: There is no fixed point. In those cases in which the course is continuous and polycyclic, one is guided by the special problems of each case. There is no harm in continuing the drug for periods of months, and we often do this.

DR. TRAVELL: In full dosage?

DR. WATSON: Yes. Once the salicylates are started, I usually continue them at the same level of dosage until the signs and symptoms return to normal. There are some exceptions in which signs of "activity" continue for periods of many months to years.

DR. TRAVELL: But what are the criteria for the cessation of therapy?

DR. WATSON: They are different in different cases. I discontinue the drugs, if there seems to be no further response.

DR. GOLD: The type of case which you described early in your discussion, Dr. Watson, was an attack of rheumatic polyarthritis, was it not?

DR. WATSON: Yes, the acute phase of rheumatic fever with carditis.

DR. GOLD: Did you intend to indicate that in such a case the salicylates produce a cure?

DR. WATSON: No, there is no evidence that salicylates cure rheumatic fever.

DR. GOLD: Do they shorten the course?

DR. WATSON: No, at the present there is no definite evidence that salicylates even shorten the course of the disease.

DR. GOLD: You believe then, that a person with an attack of rheumatic polyarthritis, with pain and swelling of the joints, fever and elevated sedimentation rate would recover just as fast whether or not salicylates are used.

DR. WATSON: This person would recover much more rapidly from the signs and symptoms if the salicylates are used than he would without them. The response of signs and symptoms is quite dramatic. But that is quite different from shortening the course of the disease for which there is no proof up



to the present time. When the drug is discontinued, in many cases the fever, the joint pains and the elevated sedimentation time return.

DR. GOLD: I take it, therefore, that you regard the salicylates as acting in rheumatic fever, in much the same way in which quinine acts in malaria. It shortens the course of an acute attack, but does not cure the disease, and there is a question whether it even shortens the course of the disease. It is a form of "suppressive" treatment.

Dr. Watson, how do Coburn's observations stand up, in which there is indication that there may be an actual cure by the salicylates?

DR. WATSON: His cases showed recurrences as did those of all other observers. The main point of Coburn's work is the prevention of cardiac sequelae, rather than that of shortening the course of the disease.

DR. GOLD: In relation to this comment of Dr. Watson's, you might be interested in this taken from Coburn's paper of 1943. This report states that of sixty-three patients used as controls, that is, having received relatively small doses of the salicylates, about 30 per cent developed cardiac involvement, whereas of thirty-eight patients who received the more intensive treatment, 10 Gm. of salicylate daily, none showed cardiac involvement. In contradistinction to this, I have here a paper published in the *Journal of the American Medical Association* by Master and Romanoff ten years previously. They gave massive doses of salicylates, doses of the same order as the intensive doses of Coburn, 8 to 12 Gm. a day or larger. There were thirty-three control cases and thirty treated with the salicylates. They found that all of the cases in both groups developed cardiac involvement, and the duration of the acute attack was practically the same in the two groups, namely, from forty-two to forty-six days. It looks to me like two groups of observers carrying out substan-

tially the same kind of treatment, came to diametrically opposite conclusions.

DR. WATSON: That is the way the matter stands. Some groups found that the salicylates prevent the cardiac complications, and others did not. A paper was published several years ago in which most of the statistics available at that time were reviewed. I do not remember the precise figures, but patients treated with salicylates in the range of dosage used by Coburn, showed a greater percentage of cardiac complications than the untreated ones. I do not believe that Coburn followed his cases long enough to be sure of cardiac complications. The evidence of valve damage may not appear until a year or more elapses after the patient becomes clinically "inactive."

DR. GOLD: You think then, that salicylate treatment is simply for the purpose of relieving symptoms.

DR. WATSON: At the present time we have no evidence of anything more than that.

DR. GOLD: Dr. Wilson, do you agree?

DR. MAY G. WILSON: I agree.

DR. McKEEN CATTELL: Do the persons who use large doses of salicylates in excess of those necessary to produce maximum analgesic and antipyretic actions, have any theories as to the mechanism of action of these larger doses?

DR. WATSON: Coburn's theory suggests that it interferes with an antigen-antibody interaction which is the factor giving rise to the specific reaction of the tissues characteristic of rheumatic fever.

DR. GOLD: Would you care to make any remarks on the special problems in children?

DR. WILSON: Rheumatic fever is a systemic disease characterized by injury to the mesodermal structures throughout the body, with special affinity for cardiovascular structures. It attacks the tendons, joints, synovial membranes subcutaneous tissues, the blood vessels, the viscera giving rise to hepatitis and nephritis, the nervous system,

and the heart causing myocarditis, valvulitis and pericarditis. As you know, children relatively infrequently develop arthritis; their chief manifestation of acute rheumatic "activity" is more often carditis. Salicylates lower the temperature to near normal levels in active carditis as in polyarthritis.

DR. WATSON: That is quite true. Children often tolerate fairly high doses of the salicylates.

DR. WILSON: Care must be used in children when using massive doses. There have been many fatal cases reported. You omitted chorea in your discussion. Do you not consider it one of the major manifestations of rheumatic fever?

DR. WATSON: You are correct; it should be included.

DR. WILSON: Do you not use the salicylates for chorea?

DR. WATSON: No.

DR. WILSON: We use sedatives to diminish the choreiform movements. Phenobarbital and rest in bed are sufficient in most cases. Occasionally, we use codeine or chloral hydrate. Sometimes we have to put up protection on the sides of the bed to prevent a child from falling out. Occasionally, there is difficulty in swallowing which requires special nursing attention.

The diet is important, and if the illness is protracted, as it is in many of these children, special attention is given to the well balanced diet and easily digested foods. Vitamin supplements, especially vitamin C, are desirable.

DR. WHEELER: I would like to ask Dr. Wolff a question. What is his opinion as to the rôle of rheumatic infection in the so-called Sydenham's chorea which we see on our wards.

DR. HAROLD G. WOLFF: I think practically all of them are related to rheumatic fever. Less than half of them develop carditis.

DR. WHEELER: In our medical wards, we

have often made the diagnosis of Sydenham's chorea in adults without other evidence of rheumatism, and then more intensive study revealed a nervous disorder which may have been responsible for the choreal movements. I am often not entirely satisfied that these cases have rheumatism.

DR. WOLFF: A problem is presented by the adventitious movements of tension and tic, and those associated with Graves' disease, especially in adolescents. But the criteria for Sydenham's chorea are reasonably sharp, and its relation to rheumatic fever is rather close.

DR. GOLD: I do not believe you are likely to see a long standing Sydenham's chorea without elevated sedimentation time, leukocytosis or fever.

Dr. Wilson, do I understand, that if a child presents itself with an active rheumatic carditis without polyarthritis, you would apply the same regimen of salicylate therapy as for the case of polyarthritis?

DR. WILSON: Yes. I would also use digitalis for the cardiac failure when it appears during rheumatic carditis.

DR. GOLD: I am assuming, of course, from all of the discussion which we have had, that in such a case the salicylate would be continued only so long as it appears to be controlling symptoms, that it would be discontinued as soon as it becomes apparent that the drug is not adding to the general comfort of the patient, although one still needs to consider the point that the salicylates may prevent pericardial or pleural effusions which sometimes become troublesome in these cases.

Is there anyone who objects to the use of digitalis for the heart failure of active rheumatic carditis?

VISITOR: It was mentioned on rounds this morning that at a recent pediatric convention, several pediatricians from various hospitals stated that digitalis is contraindicated in the heart failure of active rheuma-

tism. It appears that we are the only pediatric service in the city of New York which uses digitalis in this condition.

DR. GOLD: Was the reason stated?

VISITOR: It is believed that digitalis produces more toxic than therapeutic effects in these cases.

DR. GOLD: That does not surprise me. It is probably related to the point which Dr. Watson made earlier in his remarks, namely, that heart failure caused by active rheumatic carditis does not usually show the striking response to digitalis seen in heart failure from other causes. A patient with active rheumatic carditis may show cardiac failure progressing, even while lying in bed and fully digitalized. It is not at all uncommon to see such patients develop edema of the legs which increases from the ankle up to the abdomen, while they are receiving full doses of digitalis. It is clear that a severe active rheumatic process may in some way counteract the therapeutic effect of digitalis. It may so damage the heart that the muscle loses its capacity for improved contraction by the drug. That does not seem to be specific for the active rheumatic process because heart failure occurring in milder forms of rheumatic carditis responds fairly well to the therapeutic action of digitalis. On the whole, however, these patients do not respond as well as others, and because the rhythm is usually a sinus tachycardia rather than auricular fibrillation, they present no satisfactory guides to the degree of digitalization. In such cases, the dose is apt to be increased in the endeavor to secure better therapeutic results, and before long toxic symptoms appear. I think this is the reason why the incidence of digitalis toxicity is so high in heart failure with rheumatic carditis. As far as the evidence goes, there is no inherent danger in the drug; in these cases it is simply a matter of not knowing quite when to discontinue or reduce the dose until signs

of toxicity appear. Would you agree with that, Dr. Watson?

DR. WATSON: I think that is quite true. The electrocardiogram is one of the few guides to dosage of digitalis in these cases. Frequent tracings are of great help in detecting toxic manifestations.

DR. GOLD: There is much misunderstanding as to the use that can be made of the electrocardiogram as a guide to the dosage of digitalis in patients with rheumatic fever. Its utility here is very limited. Digitalis produces a characteristic type of RT-T change in the electrocardiogram, which is often quite different from the T-wave change resulting from the rheumatic disease itself, although there are instances in which the rheumatic disease produces a change indistinguishable from the effect of digitalis. The first problem, therefore, is that of being certain that the change is due to digitalis. But when we have answered that question, our troubles are not yet over. There still remains the question as to the significance of the change in the RT-T segment with respect to the degree of digitalization. Does the change signify that the patient has had enough digitalis, or is in need of more, or has already had too much? Here is where the electrocardiogram fails us, for in some cases a full dose of digitalis produces very little change in the RT-T segment, while in other cases only a fraction of the amount necessary to produce the full therapeutic effect is enough to produce considerable change in the RT-T segment. In the majority of cases it is safe to assume that the patient has had large enough doses of digitalis if the drug has produced fairly marked depression of the R-T segment with deep inversion of the T-wave. If sufficient improvement of the heart failure has not occurred at that point, it is unlikely that larger doses of digitalis will prove any more useful.

The P-R interval of the electrocardiogram also presents a problem in relation to digitalis. In the patient without active carditis, it is usually possible to give the full therapeutic dose of the drug to control the heart failure without significant prolongation of the P-R interval. In the patient with active carditis, however, the disease affects the A-V conduction and makes it more sensitive to the action of digitalis. In these cases, varying degrees of block may be produced by doses of digitalis which may not be sufficient to relieve the heart failure. Thus, it is that prolongation of the P-R interval which in the absence of active carditis might serve as a satisfactory indication of profound digitalization, becomes no longer useful for that purpose in the presence of active carditis.

There is, of course, the fact that the electrocardiogram serves very well in revealing toxic rhythms produced by digitalis.

DR. WILSON: We should bear in mind that digitalis is not an antirheumatic drug, and that the disease may grow worse with heart failure increasing, even when full therapeutic doses of the drug are given. The mistake lies in increasing the dose until toxic symptoms appear in these cases.

DR. GOLD: Would you suggest perhaps that the dosage of digitalis in patients with active carditis be arranged according to some schedule without reference to immediate signs of improvement? It would involve the same principle as the schedules of treatment in syphilis. All patients would be treated by a dosage plan having the highest potentiality for improvement and lowest risk of toxicity without varying the system significantly from case to case.

DR. WILSON: That is essentially the system I follow.

DR. F. HOMBURGER: I was very much interested in Dr. Watson's remarks concerning the effect of sodium salicylate on the sedimentation test, namely, the fact that

the sedimentation time returns to normal when the drug is given and becomes elevated again when the drug is discontinued. I have observed several cases of febrile conditions and cancer, in which toxic doses of sodium salicylate lower the sedimentation time to normal. There was a recent report on this subject. Since this is so, I wonder whether, once salicylate treatment is started, the sedimentation rate does not lose its value as a guide to the presence of the rheumatic infection.

DR. WATSON: It is well known that the sedimentation rate is not specific. It is also clear that when the sedimentation time returns to normal during the use of the salicylates, it may rise again when the drug is discontinued, and, therefore, the drug does not cure the disease. Even though it is a poor index at best, we do not have any better one. The white blood cell count is not nearly as useful a guide.

DR. GOLD: Are there any other questions?

DR. MORRIS PEARLMUTTER: What about the value of the anti-streptolysin titer as a guide to rheumatic activity?

DR. WATSON: It does not follow the course of the disease process.

DR. PEARLMUTTER: Does it not represent "activity" when it is markedly elevated?

DR. WATSON: Oh, no!

DR. GOLD: Dr. Wilson, what about the anti-streptolysin titer?

DR. WILSON: I agree that it has little value. It only means that the patient at some time had a streptococcic infection.

DR. PEARLMUTTER: Would that also be true if there were a sudden change in the level of the titer, let us say, a sudden rise from 200 to 800 units per cc.?

DR. WILSON: No matter what the change was. All it reflects is a streptococcic infection. It has nothing to do with rheumatic fever, in my opinion.

DR. GOLD: Even though the anti-streptolysin titer may have no meaning with

respect to the specific cause of rheumatic fever, there is the observation that a high titer is more apt to occur in rheumatic polyarthritis than in, for example, rheumatoid arthritis. Would the finding of a high titer in a case in which the problem of a differential diagnosis exists, prove helpful in arriving at a decision?

DR. WILSON: No, there are several studies showing that in rheumatic fever the titer is not more often elevated than in non-rheumatic subjects experiencing streptococcal infections.

DR. SEYMOUR RINZLER: In relation to the congestive heart failure occurring in these cases, has Dr. Watson any experience with the mercurial diuretics used alone for the control of the failure?

DR. WATSON: Our patients in this condition are routinely digitalized. I do not recall having used the mercurial diuretics alone.

DR. OVIDIO MIQUEL: There is an article in the *New England Journal of Medicine*, in November 1945, on the treatment of rheumatic fever with a calcium double salt of benzoic acid and succinic acid benzyl ester, which suggests that it may be more effective than salicylates.

DR. WATSON: That is the paper by Gubner and Szucs. It is the only report on this subject that I know. I have no experience with it. I know of no one who has corroborated it.

DR. GOLD: Is there anyone here familiar with that work?

DR. WATSON: It is possible that benzoic acid might have a slight effect in relieving symptoms.

DR. GOLD: The authors stated their belief that the benzoic acid component played little part in it since the total daily dose of the acid was less than 2 Gm. The compound was given in daily doses of from 4 to 5.3 Gm. They attributed its efficacy to the succinic acid fraction, and postulated that since this compound is a very active reducing sub-

stance, it may help to maintain cytochrome in a reduced form and prevent inactivation of other respiratory enzymes. They take the position that there is evidence for a widespread oxidative inactivation of enzymes in rheumatic fever. The results they described are dramatic, but then, the results of the treatment of rheumatic fever present such strange contrasts in the hands of different observers.

DR. WATSON: It certainly does.

VISITOR: We see many patients who seem to feel quite well two months after an attack of rheumatic fever, but the sedimentation time remains elevated. What should we do in regard to their physical activity?

DR. WATSON: I believe their physical activity should be restricted until evidence is obtained from the sedimentation rate, and from other guides such as frequent electrocardiograms, that the disease has subsided.

DR. GOLD: I wonder if Dr. Wilson would enlarge a bit on the problem of rest in bed, when to start and when to stop bed rest.

DR. WILSON: The general rule is that the child with active rheumatism belongs in bed. It is quite a problem, however, to decide when to let them out of bed. In general, this may be done when all constitutional signs or symptoms have subsided, fever, leukocytosis, elevated sedimentation rate and signs of diminished cardiac reserve. In the case of those who receive the salicylates, a week or more should elapse without the drug before the child is allowed up and about, since the salicylates may suppress the evidence of the active disease and symptoms and signs may return when the drug is discontinued.

The child who is normal in every respect except for the elevated sedimentation time, presents a special problem. I usually let them up and about, and in the course of many years of experience with this practice, I have had no reason for changing it. A thorough search in these cases sometimes

discloses an enlarged lymph node, a post-nasal discharge, sinusitis or some other cause for the elevated sedimentation time.

VISITOR: If a child has intermittent mild joint pains, but without fever or leukocytosis, do you keep such a one in bed?

DR. WILSON: Such a child belongs in bed during the periods when there are joint pains.

DR. CATTELL: How long is the period of bed rest in the average cases?

DR. WILSON: It varies widely. I know patients with severe carditis in whom the period of bed rest required was only a matter of weeks, and others who had to be kept in bed for a year or two.

DR. CHARLES WHEELER: Dr. Wilson, it has recently been fashionable to question the value of bed rest. Is there any doubt in your mind that it is necessary?

DR. WILSON: As long as the rheumatic process is active, the child should stay in bed. It is my experience that when these children are not under proper supervision and are allowed up and about, they develop increasing symptoms of heart failure.

DR. CATTELL: Do you encounter any complications as a result of the child being in bed?

DR. WILSON: Do you mean psychiatric troubles, difficulties in adjustment?

DR. GOLD: Phlebitis, or pulmonary complications.

DR. WILSON: No, I have never observed that in any child that I can recall.

DR. GOLD: In the matter of keeping the child in bed, it seems to me necessary to decide the question, which is more harmful, to be jumping about in bed, or jumping about in the room. It is not easy to keep them at rest in bed.

DR. WILSON: I think good nursing takes care of that.

DR. GOLD: Would Dr. Wilson say a word about the matter of changes in climate in the management of rheumatic fever?

DR. WILSON: The idea in a change in climate is to prevent respiratory infections which are considered to bear some relationship to rheumatic recurrences. It is desirable to have the patient in a section of the country where respiratory infections are infrequent, where the temperature is mild, and does not show wide fluctuations. If the parents can conveniently take up permanent residence in such an area, it is well to do so. The evidence of its value, however, is not sufficiently strong to justify undue financial hardships in making this change. A change in climate for only a month or two is not advisable. In the case of those families who can manage just as well living in Tucson, Arizona, as in New York City, I sometimes recommend that they move to Tucson. A place like Miami, Florida, does not seem to offer very much. There many of the dwellings are not constructed for all-year round residence; there may be no central heating; and there is a long rainy season. It is the general experience that rheumatic recurrences are as likely to occur there as in New York City.

DR. GOLD: I believe that this question has already been answered in one form or another, but I am still troubled with the possibility of a misunderstanding. Assume a patient ill in bed with active rheumatic carditis and a high fever, and when you give him moderate doses of the salicylates, he shows considerable intolerance to them; he develops profuse sweating which keeps his clothes constantly soaked, his stomach is upset, and there is an unpleasant ringing in the ears. It is true that the temperature is lowered a degree or two, but there appears to be so much unpleasantness connected with it. Would you object to discontinuing the salicylates in such a patient?

DR. WATSON: I would switch to aminopyrine.

DR. GOLD: Suppose the aminopyrine succeeded in lowering the temperature a de-

gree or two, but the patient continued to look and feel substantially as ill as he did before. Would you be inclined to continue the drug because of this effect on the fever even though there seemed to be no other beneficial effect apparent? So often we see these drugs continued for long periods of time without signs of making the patient feel better, and sometimes making them feel worse, even though the general range of the temperature is lower.

DR. WATSON: I think that lowering the temperature two degrees might be of some benefit.

DR. CATTELL: As I understand Dr. Gold's question, would it be desirable to try to obtain that result if the patient is reasonably happy without the drug?

DR. WATSON: We should not continue any of these drugs if after a reasonable trial it is clear that the signs and symptoms are not improving, for there is no good evidence that the basic course of the disease is influenced by them.

DR. GOLD: Therefore, if the patient does not begin to feel better, we should discontinue them, and let the disease run its natural course.

DR. WATSON: I agree with that; if the drug is given a sufficiently long trial in adequate dosage, and provided there are no changes in the patient's condition to indicate he was worse after discontinuing the drug. Otherwise, the drug should be started again.

VISITOR: Could we have a little more discussion of the use of the sulfonamides in prophylaxis? Dr. Watson said they were valuable for prevention.

DR. DAVID P. BARR: It is not clear to me why patients with acute rheumatic fever who have improved but are not yet entirely well should suffer a recrudescence of the disease after the sulfonamides. Is there any reason for that?

DR. WATSON: I know of none.

DR. BARR: I believe the evidence is about equally strong for penicillin producing a recrudescence.

DR. WATSON: The report by Foster in the Air Force study showed that patients with rheumatic fever did not take penicillin well and that the disease was aggravated. In our own study with relatively few cases, there seemed to be no difference.

VISITOR: Will any of the sulfonamides do?

DR. WATSON: I do not know of any experience with sulfathiazole or sulfapyridine.

VISITOR: Is there any danger in the patient becoming drug-fast as the result of the prophylactic use of sulfa in rheumatism so that it would fail to act effectively when the need for it arises in connection with some other disease?

DR. WATSON: It is not the patient who becomes drug-fast but the organism. The drug is not effective against drug-fast organisms.

DR. GOLD: Dr. Wilson, what are your views on sulfa prophylaxis of rheumatism?

DR. MAY G. WILSON: I do not believe there is any satisfactory evidence that the sulfa drugs prevent rheumatic recurrences. There are several studies which indicate that a streptococcal infection is one of the factors responsible for recurrence of rheumatic fever, and it was hoped that by preventing these infections, the recurrence of the rheumatism might be prevented. Unfortunately, however, the studies were not so planned as to make an evaluation possible. The numerous variables were not taken into consideration. It has been shown that the risk of recurrence varies with the age of the child and the time that has elapsed since the last attack. These factors were not considered in the studies on sulfa prophylaxis. Also, they failed to examine the problem by the alternate case method which tends to eliminate bias in selection.

DR. WATSON: I disagree with Dr. Wilson in regard to the value of sulfa prophylaxis.

It is true that some of the studies were not very well controlled, but Dr. Kuttner's in particular, have been about as well controlled as possible in such a problem; they took into consideration the factor of age and number of previous attacks. The difference between the results in the control and treated groups was quite significant.

DR. WILSON: I cannot agree with Dr. Watson's view that Dr. Kuttner's cases were adequately controlled. Although she did try to match cases by age, the alternate case method necessary to eliminate bias in selection was not used. The factor of the length of time elapsing since a previous attack of rheumatism was not satisfactorily applied. This is of the greatest importance. In estimating the natural risk of recurrence, we found that the person who has had an attack during the previous year, has three times as great a chance of a recurrence as the one who has not had an attack for a year. When we applied our methods of analysis to Dr. Kuttner's control group of patients, we learned that there were far more recurrences there than were to be expected. It was evidently, therefore, a biased group, and hence the fact that there were fewer recurrences in her treated group cannot be accepted as representing a significant effect of the drug.

DR. BARR: Is the danger in the use of sulfadiazine a factor in restraining Dr. Wilson from using it in the prophylaxis of rheumatism.

DR. WILSON: No, there simply is no evidence that convinces me that the sulfa drugs have prevented recurrences. In all the published studies in civilian life, I find the same difficulty in evaluating the results. Until a properly controlled study is done which demonstrates that sulfa drugs can prevent rheumatic recurrences, I see no justification for this routine practice. At the present time, its use should be limited to experimental investigations.

DR. GOLD: I think that Dr. Wilson's point about controls is a very important one, namely, the fact that the time which has elapsed since the last attack of rheumatism is a factor determining the likelihood of a recurrence. Clearly, if the group used as controls all had an attack last year, and the sulfa-treated groups have gone two years without an attack at the time that they were put into the study, the results might show a much higher incidence of recurrence in the controls than in the treated cases. But these results would be deceptive. According to Dr. Wilson, that is what would be expected in two such groups even if both were untreated with sulfa. I might add that Dr. Messeloff made a serious attempt to test the value of sulfa prophylaxis in our children's cardiac clinics, and was unable to detect any difference between treated and untreated cases.

DR. SAMUEL Z. LEVINE: There is clearly an unsettled controversy regarding the effectiveness of sulfonamide therapy as a prophylactic measure in rheumatism. The bulk of opinion favors it. I have spoken to Dr. Paul and a number of persons who have used sulfonamide therapy as a prophylactic procedure, and they all appear to be enthusiastic about it. Dr. Wilson's objection on the grounds of inadequate controls, I think, leaves the evidence inconclusive.

DR. CATTELL: I wonder how the proponents of the prophylactic use of sulfonamides explain the failure of the drug to benefit the disease after it has started.

DR. WATSON: It is a fact that the drug is of no benefit after the disease has started, and during the active stage it may aggravate the disease.

DR. LEVINE: Dr. Coburn once told me that if you give the sulfonamides to a patient with active rheumatic fever, you are almost signing his death warrant. I think that statement is a bit strong. I do not know whether he still holds that view. I asked him



specifically whether he would give sulfonamides to a patient with pneumococcal pneumonia if he also had rheumatic fever. He said no at that time. I do not share that attitude. I do not know whether or not he has changed his.

DR. JOHN E. DEITRICK: If sulfonamide is so dangerous during the active stage of the disease, how long should one wait after an attack of rheumatic fever, before one may safely start the prophylactic therapy?

DR. GOLD: Would Dr. Watson answer that?

DR. WATSON: I think it is pretty safe to start it as soon as all signs and symptoms of active infection disappear. The sedimentation rate is perhaps the most sensitive guide. The patient should be afebrile.

DR. DEITRICK: In some cases that may mean a delay of six months or a year before the prophylactic treatment is started.

DR. WATSON: I know that Dr. Dodge has given it to patients who still had a low grade rheumatic "activity" without ill effects. Some, however, will suffer an exacerbation if the sulfonamide is given in the active stage.

DR. GOLD: What dosage of sulfa do you use for prophylaxis, 1 or 2 Gm. daily throughout the school year in children?

DR. WATSON: Usually 1 Gm. The Navy undertook a large program of sulfa prophylaxis. The incidence of streptococcal infections and meningitis was greatly reduced, and the incidence of rheumatic fever was correspondingly diminished until sulfadiazine-fast strains of streptococci appeared when the rates of streptococcal infections and rheumatic fever promptly increased again. The Air Force of the Army tried it with the same general results. Sulfadiazine is undoubtedly the best of the drugs for this purpose, although I think that sulfanilamide was chiefly used in the civilian studies.

DR. GOLD: What proportion of patients develop toxic symptoms as the result of this treatment?

DR. WATSON: It varies a great deal among the different studies, from less than 1 per cent in some to as high as 10 or 20 per cent of the cases in others. As far as I know, there has only been one death reported in civilian practice. In the Navy there were a few deaths, the exact number I do not know, but I am sure the incidence of toxic reactions was very low and, of course, the death rate was extremely low.

DR. GOLD: I have a paper here published in the *Journal of the American Medical Association* in 1940 on the treatment of rheumatic fever. All of the following suggestions for treatment are offered: streptococcus vaccine by intravenous injection, typhoid vaccine by intravenous injection, antistreptococcus serum, iron, potassium arsenite and prophylactic vaccination against recurrence. Dr. Watson, would you use any of these in your regimen for treatment?

DR. WATSON: No, I do not think I would.

DR. GOLD: We may now summarize the chief points which were discussed in the conference this afternoon. Rheumatic fever is a chronic febrile disease involving the mesodermal structures of the body. It shows acute phases and frequent recurrences. There are numerous clinical varieties depending on the structures which are predominantly involved, the chief ones being polyarthritis, carditis and chorea. The form with polyarthritis is most common in adults, and with carditis, most common in children.

There is no specific cure, but the salicylates play an important part in its treatment. There is an unsettled controversy concerning their dosage, and the question as to whether they act merely to relieve symptoms or alter the basic development of the disease. The consensus appears to be that the salicylates are "suppressive" and not curative, in much the same sense as quinine is "suppressive" in malaria. In an acute attack, under suitable doses, pain is promptly relieved, fever subsides, effusions

into joints and other cavities diminish, and the blood sedimentation time may return to normal. However, when the drug is discontinued, the signs and symptoms reappear, showing in this respect the same tendencies as in the untreated case. The "acute attack" should be distinguished from the entire "disease"; there appears to be no proof that the course of the "disease" is shortened by the salicylates. The recent revival of the belief that massive doses of salicylates given intravenously, beyond those necessary to control signs and symptoms, may prevent the development of heart disease, has not been confirmed.

Aminopyrine and cinchophen may be employed for the same purpose in patients who cannot tolerate salicylates, although their inherent toxicity is greater and are, accordingly, not advisable for routine use.

Sodium bicarbonate may be given with the salicylates to relieve gastric distress. The old controversy concerning its effect on the blood level of salicylate and the excretion of salicylate seems now to be settled by the more recent studies which are in accord in showing that the blood level of salicylate is lowered and the urinary excretion is increased by sodium bicarbonate. This fact, on the one hand, tends to diminish the efficacy of the salicylate, but may, on the other hand, be applied to the treatment of salicylate poisoning.

The details of systems of dosage for the salicylates and the other antirheumatic drugs were discussed.

The much debated question of digitalis in heart failure caused by rheumatic carditis

was explored. Opinion is still sharply divided; there are those who believe that it does more harm than good, and those who believe it should be used routinely. There seems to be little doubt that the therapeutic response to digitalis in these cases is quite limited. It was suggested that in active carditis, digitalis be used in accordance with a schedule of dosage with the greatest potentiality for therapeutic effects and least likelihood of toxic effects, without change in doses in relation to the immediate therapeutic results in any particular case, in much the same way as the arsenicals are used in the treatment of syphilis. This would prevent the increase in dose to the point of toxicity as is so often the practice.

The controversy concerning the prophylactic value of sulfadiazine received considerable attention, there being those who use 1 Gm. daily throughout the school year to prevent recurrences, and those who regard this practice without sufficient proof of value. The numerous control factors which have to be taken into account in a study of the value of drugs in rheumatic fever were described.

Many other points of interest were discussed, such as the danger of the pericardial tap, the use of vitamin K to control epistaxis, the value of bed rest and the factors determining the duration of bed rest, the value of a change in climate to prevent the recurrence of active rheumatism, the use of the electrocardiogram as a guide to digitalis action in rheumatic fever and the anti-streptolysin titer as a guide to rheumatic activity.

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# Clinico-pathological Conference

## Hypertension and Renal Failure\*

**S**TENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

**T**HE patient, D. D., a nineteen-year white married housewife, entered the Barnes Hospital on July 30, 1946, complaining of fatigue, headache, vomiting, and shortness of breath. The family history was non-contributory. The patient had not had scarlet fever, rheumatic fever, frequent sore throats or other serious illnesses. Her health had been excellent until the birth of her only child seventeen months prior to admission. The pregnancy had apparently been entirely normal and the delivery and puerperium were uneventful. Her habits were good and her diet adequate; for years she had been very fond of salt and had drunk large amounts of water.

One month after the birth of her child the patient developed increasing ease of fatigability. She consulted a physician who examined her and told her that her blood pressure and urine were normal. Two months later she began to complain of frontal headaches which were often associated with nausea and vomiting. They continued to recur about three times a week and gained in intensity, but were usually controlled by medication. The headaches and weakness continued during the following year. Five months before entry the patient again consulted her family physician; he examined her urine and found white blood cells but no red cells or casts.

The red blood cell count was reported as 3,200,000.

Three months prior to admission, the patient had severe diarrhea for a few days. Shortly thereafter, a red, raised, pruritic, discrete eruption appeared transiently on the extremities. At that time, her systolic blood pressure was recorded as 110 mm. of mercury. Subsequently "black and blue spots" developed on her extremities and these continued to appear. Shortly before admission she developed shortness of breath at night which was relieved when she sat up. Her systolic blood pressure rose to 220 mm. of mercury. Because of dull epigastric pain, headache, vomiting and shortness of breath she was admitted to the hospital.

At the time of entry, the patient's temperature was 36.9°C., pulse 110, respirations 22, and blood pressure 200/140. She was acutely ill and appeared much older than her stated age. She was able to lie in bed comfortably using only one pillow; she answered questions slowly and with difficulty. There was a brown discoloration of the skin of the face and palms but none of the mucous membranes. Over the arms and legs ecchymoses of various sizes were seen. The eyes were prominent and staring, and the palpebral fissures were widened. Two petechial spots were present in the conjunctivae. The pupils reacted normally. There was marked bilateral papilledema,

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† By Robert J. Glaser, M.D.

and exudates and hemorrhages were seen in both fundi. The arterioles were narrow and tortuous. Examination of the upper respiratory tract was negative. The buccal mucous membrane was pale. The breath was not uremic. Arterial pulsations in the neck were prominent. The lungs were clear. The entire precordium heaved with each heart beat. A visible impulse was seen in the fifth left interspace in the anterior axillary line, and at the apex there was a soft systolic thrill and a grade III systolic murmur. A diastolic gallop rhythm was audible. The aortic second sound was accentuated. The liver edge was palpable 6 cm. below the right costal margin; the edge was sharp and tender. There was tenderness also in the epigastrium. The spleen was palpable 3 cm. below the costal margin. Pelvic examination revealed nothing abnormal. There was no edema. The neurological examination revealed no abnormalities.

The laboratory studies were as follows: Blood count: red cells, 2,700,000; hemoglobin, 8.5 gm.; white cells, 13,300; differential count: basophiles, 1 per cent; segmented forms, 75 per cent; lymphocytes, 19 per cent; monocytes, 5 per cent. Urinalysis: albumin, +++; casts, 0; sediment, occasional red blood cell per high power field. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 90 mg. per cent; chlorides, 82 meq/liter; total proteins, 5.8 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 2.7 Gm. per cent; CO<sub>2</sub> combining power, 41.5 vol. per cent; calcium, 7.5 mg. per cent; phosphorus, 14 mg. per cent. Phenolsulfonphthalein test: no dye excreted in one hour. Circulation time (decholin): 15 seconds. Venous pressure: 80 mm. NaCl. Antifibrinolysin test: negative. Aschoff-Zondek test: negative. Electrocardiogram: T wave isoelectric in lead I. Interpretation: myocardial damage. Roentgenogram of the chest: "Heart and aorta

are within normal limits. The lung parenchyma is clear."

On admission, the patient was given 1.2 mg. of digitoxin orally and one liter each of  $\frac{1}{6}$  molar sodium lactate solution and 5 per cent glucose in water intravenously. She also received 500 cc. of red cell residue. She became quite drowsy and developed Cheyne-Stokes respirations. On auscultation crepitant râles were heard at both lung bases. The patient vomited frequently. During her first week in the hospital no other important changes occurred.

The patient then had a clonic convulsion which was controlled with intravenous magnesium sulfate. Subsequently she had similar convulsions repeatedly. The blood non-protein nitrogen had risen to 148 mg. per cent; the chlorides had fallen to 71 meq/liter and the CO<sub>2</sub> combining power was 45.2 volumes per cent. The red blood cell count was 1,670,000. The breath became urinous. Drowsiness increased and there was occasional muscle twitching. At the end of the second hospital week sacral edema appeared. The blood chlorides had continued to fall, reaching a level of 55 meq/liter and the non-protein nitrogen was 178 mg. per cent. Supportive treatment with 5 per cent glucose and  $\frac{1}{6}$  molar lactate was continued, but during the third week the blood chlorides were only 49 meq/liter; thereafter they remained at levels of that order. The venous pressure, which had been normal, rose to 235 mm. NaCl. Edema of the legs and face appeared and a pericardial friction rub was heard at the apex. Stupor, increased respiratory difficulty and intractable cardiac failure were terminal events. At no time was the temperature elevated.

#### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: The case which we are to discuss presents a puzzling diagnostic problem. This nineteen-year old

woman had an apparently negative past history and a seemingly normal pregnancy, delivery and puerperium. One month after the birth of her child, she began to have symptoms of the disease which led to her death about fifteen months later. Dr. Schroeder, would you suggest a diagnosis.

DR. HENRY A. SCHROEDER: Chronic glomerulonephritis comes to mind first but there are several facts against that diagnosis. The patient's symptoms appeared at a time when her urine was said to have been negative and her blood pressure normal. Such a sequence of events is unusual.

DR. ALEXANDER: I should like to make an addition to the record. In the protocol it is stated that when the patient first became ill and consulted her physician, he told her that her blood pressure was normal; actually, it was 136/90. I think this information is important. It is your opinion then, Dr. Schroeder, that this patient probably had chronic glomerulonephritis?

DR. SCHROEDER: Yes, but I cannot explain the normal urine at the time when she first became ill.

DR. EDWARD MASSIE: I believe the history, findings and course are compatible with chronic pyelonephritis. A normal urine, except for a low specific gravity, may be found in chronic pyelonephritis, even in the terminal stages; I agree with Dr. Schroeder that in glomerulonephritis the urinary findings should be abnormal. In nephrosclerosis, the urinary findings are also abnormal.

DR. ALEXANDER: And if pyelonephritis were responsible for the patient's hypertension, do you believe both kidneys were involved?

DR. MASSIE: They may have been. It should be pointed out, however, that unilateral pyelonephritis can give rise to hypertension, which in turn may lead to arteriolar nephrosclerosis.

DR. ALEXANDER: Would you estimate

the duration of the pyelonephritic process necessary to produce hypertension of the degree recorded in this case? Do you believe the pyelonephritis antedated her pregnancy?

DR. MASSIE: The pyelonephritis could have had its onset in pregnancy or immediately thereafter. It may be associated with rapidly developing hypertension.

DR. ALEXANDER: Are there any other suggestions?

DR. HAROLD A. BULGER: Rather than chronic pyelonephritis, I believe the patient may have had primary vascular disease.

DR. ALEXANDER: In other words, you would identify this process as arteriolar nephrosclerosis or malignant hypertension. In the history there is the statement that she was very fond of salt and drank a great deal of water. Has that fact any relevance?

DR. W. BARRY WOOD, JR.: I think it is very important and suggests that the patient's renal function was probably poor in that her kidneys were unable to secrete a concentrated urine. She apparently was forced to ingest large amounts of water in order to excrete sufficient urine to clear the blood of nitrogenous products. The polydipsia suggests that the patient had renal disease before she became pregnant.

The craving for salt and the very low serum chloride noted in the hospital bring to mind two cases that Dr. George Thorn reported in 1944.<sup>1</sup> Both patients entered the hospital with the symptoms of Addison's disease but were shown later to have chronic glomerulonephritis; the diagnosis was confirmed at autopsy in each case. Thorn termed the syndrome, "salt losing nephritis." Normally the adrenal cortex stimulates the reabsorption of sodium chloride from the renal tubules. In Addison's disease, the adrenal cortex fails to function, reabsorption does not take place and sodium chloride is excreted in excessive amounts. In "salt losing nephritis," the difficulty is not in the adrenal cortex but in the renal

tubules; the end result is the same in that salt is not properly reabsorbed and is thus lost in the urine. Thorn points out that while Addison's disease may be simulated clinically, "salt losing nephritis" will not respond to adrenal cortical extracts because of the site of the pathologic lesion.

DR. ALEXANDER: Dr. Allen, will you comment on the relationship of the patient's pregnancy to the underlying disease.

DR. WILLARD M. ALLEN: First of all, if this patient had had chronic glomerulonephritis, I think it very unlikely that she would have died a year and a half after her pregnancy without having had complications during her pregnancy. It is well known that chronic glomerulonephritis is reflected in pregnancy by hypertension which appears quite early; fetal death in utero at about six or seven months is not uncommon. This patient apparently went through her pregnancy without any difficulty. One month postpartum her diastolic pressure was 90 mm. of mercury. Certainly such a diastolic blood pressure is distinctly abnormal in an apparently healthy young girl of nineteen, but it does not afford much assistance in the problem of deciding whether this girl had chronic glomerulonephritis. We often see patients with chronic glomerulonephritis who have a blood pressure of this order at the beginning of pregnancy; it may rise gradually during the course of the pregnancy and even though such patients may lose the fetus in utero, they may have a blood pressure of only 135/90 four weeks after delivery.

The other suggestion which has been made, i.e., chronic pyelonephritis, may be commented on a little more extensively. In the practice of obstetrics, it is not uncommon to see a patient, who has an episode of acute pyelonephritis in pregnancy, go to term without developing any sign of toxemia. Recently we had a patient on our service who had been seen in the obstetric

clinic in the seventh month of pregnancy with frank hematuria. She was seen in consultation by the urologists in regard to the possibility of a renal stone but that diagnosis was not established. Her systolic blood pressure was normal; the diastolic pressure was 90 mm. of mercury. The medical student, to whom the patient was assigned in the clinic, did a phenolsulfonphthalein test and drew blood for a non-protein nitrogen determination. Unfortunately, the patient left the clinic and was not seen after the laboratory findings were reported. When she was admitted to the hospital two weeks later, the fetus was non-viable; her blood pressure was unchanged. In checking the clinic record, it was found that the phenolsulfonphthalein excretion determined two weeks before had been zero and the non-protein nitrogen had been 100 mg. per cent. Her urine showed only red blood cells in the sediment. The patient died two weeks after entry in uremia; terminally her blood pressure had risen to much higher levels. At autopsy, she had chronic pyelonephritis of long duration.

Thus, in the case we are discussing today, the relatively unimpressive past history does not rule out pyelonephritis. We are told the patient did have white blood cells in the urine; this finding points to pyelonephritis. If I had to choose between chronic glomerulonephritis and chronic pyelonephritis, I would choose the latter, particularly if I believed that the patient's course had been deleteriously effected by pregnancy.

DR. ALEXANDER: Would you consider a third diagnosis, that of essential hypertension following toxemia of pregnancy?

DR. ALLEN: Although it is true that patients who develop severe preclampsia may have residual hypertension, I am not aware of ever having seen such a patient die of malignant hypertension only a year and a half later.

DR. PALMER H. FUTCHER: From reading Goldring and Chasis's book on hypertension, Dr. Allen, I gained the impression that they believe that pregnancy has very little influence on the course of chronic glomerulonephritis and that patients with chronic glomerulonephritis who became pregnant and develop toxemia do not fare any less well than other toxemia patients. Would you discuss further your views in regard to the effect of pregnancy on the course of chronic glomerulonephritis?

DR. ALLEN: I do not think that one can say pregnancy has an adverse effect on that disease any more than he can say it has an adverse effect on the course of heart disease. In general, it is believed that chronic glomerulonephritis does effect pregnancy. This seems particularly true in patients who have diastolic hypertension and albuminuria at the beginning of pregnancy. Such patients are most apt to develop severe complications. On the other hand, patients with elevated diastolic blood pressure but with no albuminuria may do quite well and are statistically more likely to go through pregnancy uneventfully. Successive pregnancies are apt to be very detrimental, however, and severe toxemia and fetal death are common.

DR. ALEXANDER: Dr. Wood brought out a very impressive feature in this case, namely, the hypochloremia. Dr. Futcher, would you comment on this finding?<sup>2</sup>

DR. FUTCHER: From Gamble's data, it is known that the serum sodium is normally higher by 15–20 meq/liter than the sum of the serum chloride and bicarbonate fractions. In this case, the total of the chlorides and bicarbonate indicates a low serum sodium; the CO<sub>2</sub> combining power was only slightly depressed and did not reflect severe acidosis; on the other hand, the chloride was very low. In kidney disease low values for the serum sodium and chloride can be explained in two ways. First,

if the kidney is unable to make ammonia by means of which a portion of the waste acids are excreted, fixed base must be used. Second, loss of sodium chloride may be due to the mechanism to which Dr. Wood referred; that is, the specific inability of the tubules to reabsorb sodium chloride from the glomerular filtrate. In this case, I would be inclined to explain the low sodium by the second factor, especially since the CO<sub>2</sub> combining power was not markedly depressed. The elevation of phosphorus, of course, points to retention of inorganic acids and speaks for acidosis.

DR. ALEXANDER: One other feature of this case was the presence of petechiae for many weeks prior to the patient's death. Are there any comments in regard to these lesions?

DR. SCHROEDER: The occurrence of petechiae is quite consistent with advanced renal disease. They are seen particularly when there is nitrogen retention, and the fact that the patient had petechiae for such a long period of time strongly suggests that she had nitrogen retention at least several months prior to entry, and possibly at the time when the anemia was discovered.

DR. LEO J. WADE: Dr. Alexander, I believe this patient could have had glomerulonephritis with a normal blood pressure which rose only in the terminal phase of the disease.

DR. ALEXANDER: Against that postulation is the fact that the patient had such advanced hypertensive neuroretinopathy.

DR. WADE: Is it equally likely that excessive salt loss could occur in any one of the three diseases we are discussing?

DR. WOOD: The patients whom Dr. Thorn reported had chronic glomerulonephritis, but the phenomenon does occur to a lesser extent in pyelonephritis and nephrosclerosis. Dr. John Peters has recorded similar blood chemical findings in both chronic pyelonephritis and malignant nephrosclerosis.

DR. ALEXANDER: Although there is not complete unanimity in regard to the diagnosis, the staff seems to favor a diagnosis of chronic glomerulonephritis. Chronic pyelonephritis and malignant nephrosclerosis would appear to be less likely possibilities.

Clinical Diagnosis: Chronic glomerulonephritis and uremia.

#### PATHOLOGICAL DISCUSSION

DR. ROBERT A. MOORE: The three major diseases which may give rise to the clinical picture observed in this patient were discussed: malignant nephrosclerosis, chronic glomerulonephritis and chronic pyelonephritis. It may be profitable to consider the features which the kidney may exhibit on gross examination which might point to the correct diagnosis. In nephrosclerosis, the surface of the kidney may be either uniformly finely granular or it may be smooth. In addition, in the malignant phase, there will be petechiae throughout the surface of the kidney and to a lesser extent in the substance of the cortex. In glomerulonephritis, the surface of the kidney is nodular but irregularly nodular; this is in contrast with the uniform character of the nodularity in nephrosclerosis. In pyelonephritis, there are U-shaped, flat-based scars that are highly characteristic. Occasionally kidneys are seen at autopsy in which pyelonephritis has progressed so far that there are no individual scars, but the entire surface is contracted and shows a very characteristic appearance of extremely fine granularity of the surface.

In regard to size, the kidney in malignant nephrosclerosis is essentially normal. In chronic glomerulonephritis, the kidneys are usually very small; indeed, the smallest kidneys seen at autopsy are those seen in patients who have died of this disease. In pyelonephritis, the kidney is usually moderately reduced in size.

The kidney pelvis in malignant nephrosclerosis is relatively normal as far as size is

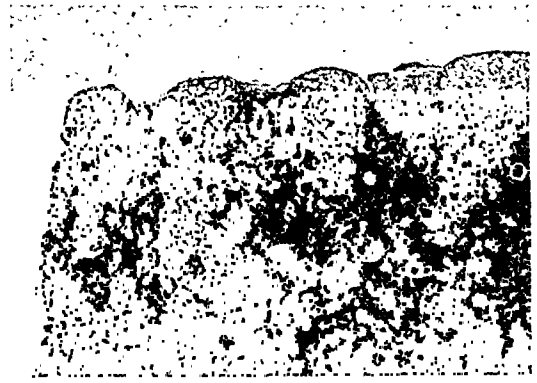


FIG. 1. A section of the cortex of the kidney showing tubular dilation and scarring with resultant nodularity of the surface. 20 X.

concerned. A few petechiae may be seen. As the kidney contracts in chronic glomerulonephritis, it contracts in all directions, and the pelvis is dilated because of the loss of renal substance. In pyelonephritis the pelvis is dilated but it is likewise deformed because of variation in degree of involvement.

Dr. Owen will now describe the significant gross findings in this case.

DR. JAMES G. OWEN: The kidneys were much reduced in size, weighing 60 Gm. each. The cortical surfaces were pale and coarsely granular; they cut with a gritty resistance, revealing smooth, firm, pale parenchyma in which the cortico-medullary boundary was not well defined. The cortex was only 4 mm. thick; no petechiae were seen. The renal pelves were slightly dilated, but the ureters were normal.

DR. MOORE: I think it is very evident that on the basis of gross examination, a diagnosis of chronic glomerulonephritis can be made.

DR. OWEN: The heart was greatly enlarged and weighed 690 Gm. The pericardium was thickened and adherent to the epicardium by tough, elastic, fibrinous adhesions which obliterated the pericardial cavity. The walls of the ventricles were thickened.

DR. MOORE: The other organs, so far as the gross examination was concerned, were normal. The diagnosis from a microscopic



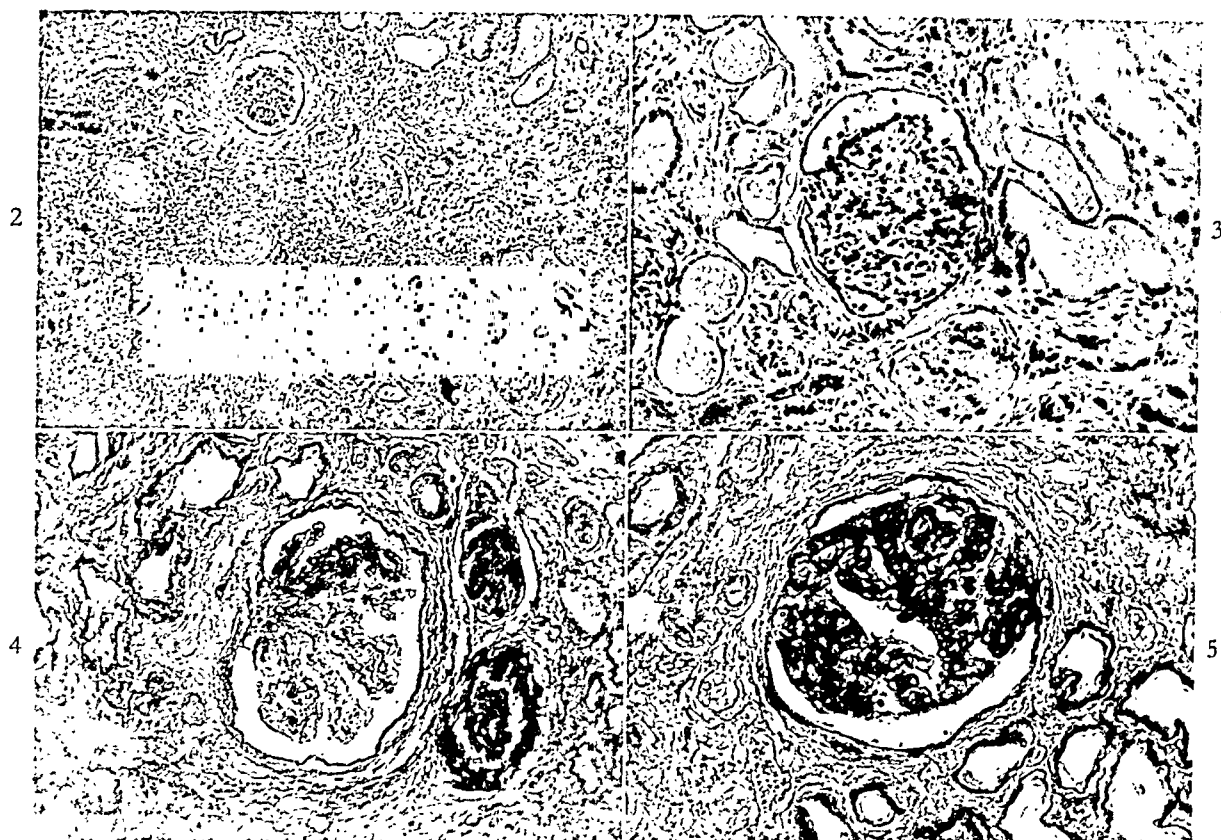


FIG. 2. Section of the renal cortex showing fibrosis, cellular infiltration and variations in the degree of glomerular involvement. 47 X.

FIG. 3. A section of the kidney showing a glomerulus with capsular adhesions and an increase in the number of nuclei. 100 X.

FIG. 4. Section of the kidney showing partial infarction of a glomerulus and thickening of the capsule; Heidenhain's stain. 100 X.

FIG. 5. Section of the kidney showing sclerosis of the capillaries in the glomerulus and capsular adhesions. 100 X.

standpoint was essentially the same as in the gross, though there are variations which will be discussed herewith.

The first section (Fig. 1) shows three nodules on the surface of the kidney. The tubules are greatly dilated and lined by epithelium of the type seen in the proximal convoluted tubules; the cells are not, however, quite so tall as normal. The depressions represent scar tissue. In this section the reason for the difference in the character of the nodularity in malignant nephrosclerosis and chronic glomerulonephritis may be seen. The former is a diffuse disease of the entire kidney and affects it uniformly; in an inflammatory process such as glomerulonephritis, the involvement varies in degree.

In Figure 2, a section of the cortex is seen. The photomicrograph shows at least six glomeruli; the pathologic change is not identical in any two. There is tremendous thickening of Bowman's capsule and an increase in the cellularity and a decrease in the lobulations of the glomeruli. One of the glomeruli is completely destroyed and replaced by fibrous tissue which is still moderately cellular. In another, glomerular adhesions are seen, and in a third, there is fibrosis of one part while the remaining part shows essentially normal structure. In general, it can be said that the more glomeruli involved, and the less uniform the involvement, the more likely the diagnosis of chronic glomerulonephritis. Therefore, from

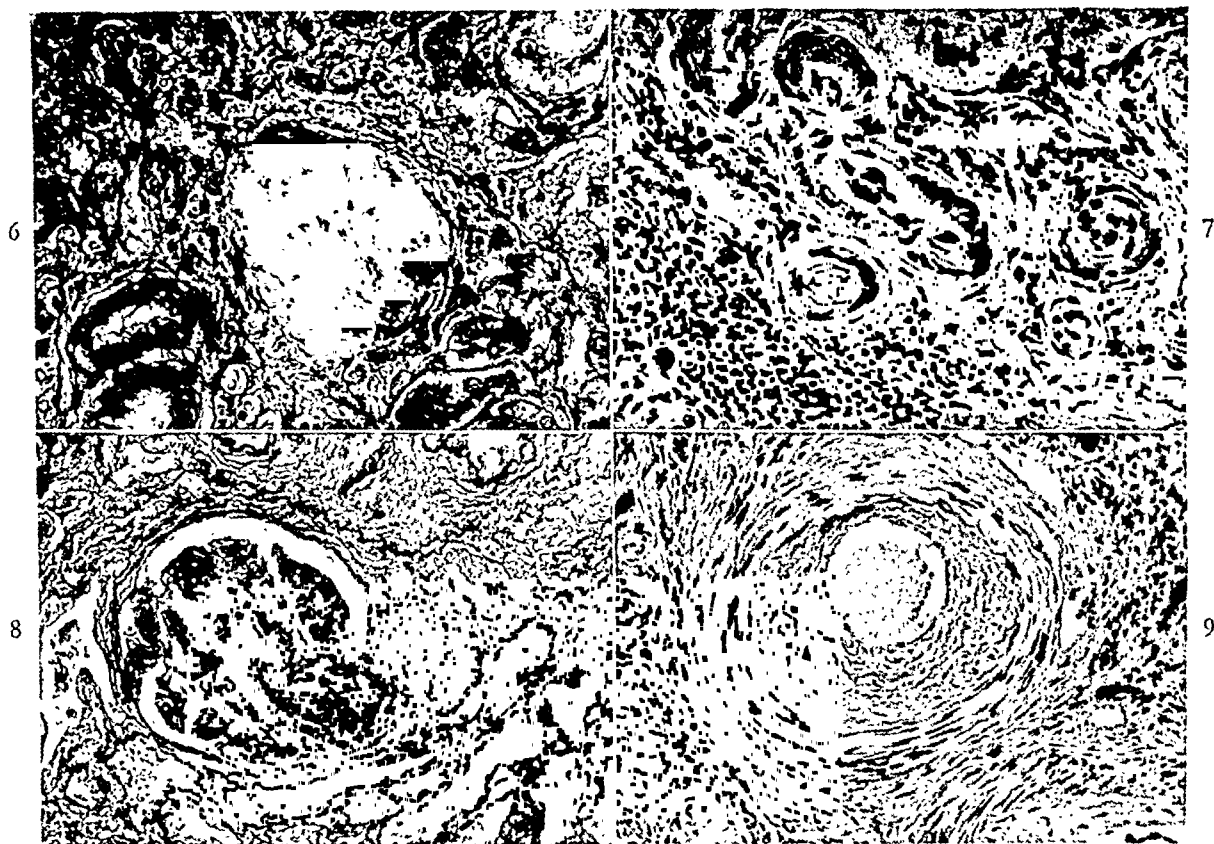


FIG. 6. Section of the kidney showing a totally obliterated glomerulus. 100 X.

FIG. 7. Section of the kidney showing several arterioles, with thickening, hyalinization of the walls and edema. 400 X.

FIG. 8. Section of the kidney showing necrosis of the afferent arteriole of a glomerulus and beginning infarction. 100 X.

FIG. 9. Section of the kidney showing a small artery in the cortex that exhibits thickening of the intima. 100 X.

this section of the cortex, the gross diagnosis of chronic glomerulonephritis may be supported. The rest of the cortex shows extensive fibrosis, destruction of tubules with flattening of the epithelium, and slight to moderate cellular infiltration with lymphocytes. The amount of cellular infiltration is not of too much value in differential diagnosis; it is extremely marked in pyelonephritis, least conspicuous in nephrosclerosis and varies considerably in glomerulonephritis.

In the next section (Fig. 3) the details of the glomerular change are shown. A typical glomerulus is seen; it shows capsular adhesions, alteration in the character of the cells lining Bowman's capsule, an increase in the number of nuclei within the glomerulus,

and adhesions between the glomerular tufts. These changes are not seen to any extent in either of the other two types of chronic renal disease discussed. In Figure 4 Heidenhain's stain for connective tissue was used; a glomerulus is seen in which one area shows advanced change while other areas show no change at all. In the next section (Figure 5) the process is more marked; the glomerulus has become a single mass, the lobules have become adherent to one another, and thickening of the basement membrane is not seen to the degree common in arteriolar nephrosclerosis. In Figure 6, a totally obliterated glomerulus with a mass of fibrous tissue containing a few cells is seen. Under higher magnification nuclei were seen in

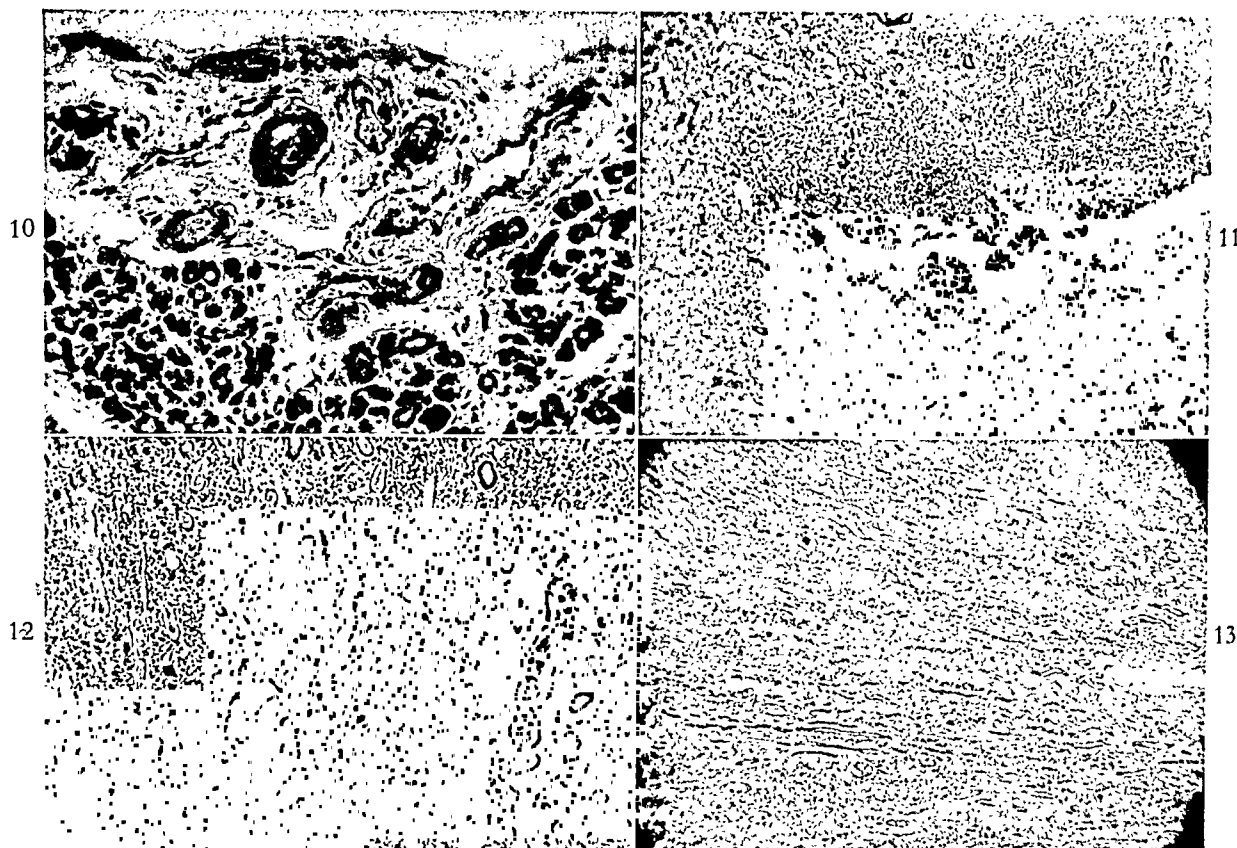


FIG. 10. Section of the pancreas showing several arterioles in the pancreas. They exhibit thickening and hyalinization of the walls as well as necrosis. 100 X.

FIG. 11. Section of the renal pelvis showing desquamation of the epithelium, lymphocytic infiltration and fibrosis. 20 X.

FIG. 12. Section of the kidney medulla showing cellular infiltration, fibrosis and hyaline casts in the tubules. 30 X.

FIG. 13. Section of the kidney medulla showing the characteristic pattern of cellular infiltration in pyelonephritis. 20 X.

the middle of the connective tissue; they would not be present if the changes were due to malignant nephrosclerosis.

In Figure 7 a group of arterioles in the kidney are seen; they are tremendously thickened and the walls are hyalinized in some areas. Each arteriole in the section shows these changes. In one of the vessels, it can be seen that the wall is edematous and occludes the lumen. This thickening of the arterioles is certainly an indication that the patient had arteriolar nephrosclerosis to at least some extent. The edema of the walls of some of the arterioles points to the possibility that the changes of malignant phase of

nephrosclerosis might be found. The next section (Fig. 8) shows an entering arteriole of a glomerulus; the wall of the arteriole has undergone necrosis and there is a thrombus in the lumen and beginning infarction of the glomerulus. In Figure 9, a small artery in the kidney is seen; it gives evidence that there was also a certain degree of arterial nephrosclerosis which may have played a part in bringing about the marked decrease in the size of the kidney. The intima is greatly thickened, the lumen is perhaps one-third normal size, but the muscularis is fairly normal. In the next section (Fig. 10) a group of arterioles in the pancreas are

shown; again there is necrosis of the wall of these arterioles. The foregoing changes allow diagnosis of both chronic glomerulonephritis and malignant nephrosclerosis to be made.

Figure 11 is a section of the renal pelvis; there is desquamation of the epithelium. There is marked infiltration of the submucosa with lymphocytes and mononuclear cells; fibrosis is prominent. These changes are characteristic of pyelonephritis. Figure 12 is a section from the medulla showing fibrosis, cellular infiltration, and numerous hyaline casts in the tubules. These changes were not seen in the sections of the cortex, but were confined to the medulla and very largely to the region immediately surrounding the pelvis. In the next section (Fig. 13) the pattern of cellular infiltration within the medulla is seen. It extends in streams between the tubules. This change is also characteristic of chronic pyelonephritis but not of the other two diseases under discussion.

From the standpoint of pathologic anatomy this patient had chronic glomerulonephritis, malignant nephrosclerosis and chronic pyelonephritis; however, there is little doubt that the most widespread lesions are those of chronic glomerulonephritis. I do not think that pyelonephritis played an important part in the patient's clinical course; the most significant disease was the glomerulonephritis; to it was added, as is so frequently the case, arteriolar disease. During the terminal stage of the illness, the patient

developed a slight degree of the malignant phase of arteriolar nephrosclerosis.

DR. ALEXANDER: In your opinion what was the duration of the chronic glomerulonephritis?

DR. MOORE: The findings are compatible with the clinical history of approximately fifteen months. However, the process may have been present for a number of years; it is difficult to be sure since the course of the disease is extremely variable.

*Final Anatomical Diagnosis:* Chronic glomerulonephritis; arteriolar nephrosclerosis, with necrosis of arterioles; chronic pyelonephritis; arteriolosclerosis, generalized; hypertrophy and dilatation of the heart (690 Gm.); ecchymoses and petechiae in the skin, lungs, pericardium, diaphragm, and mucosa of the stomach, colon and urinary bladder; organizing fibrinous pericarditis with obliteration of the pericardial cavity.

*Editor's Note:* After the conference, Dr. Willard Allen made the following suggestion, namely, that the "salt losing" phenomenon, by affording a mechanism whereby salt was lost and edema thus inhibited, may have explained the patient's apparently uneventful pregnancy.

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# Case Reports

## Carcinoma of the Prostate Gland\*

### *Report of a Patient Treated with Orchiectomy and Estrogens*

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**D**URING the past decade carcinoma of the prostate gland has been subject to biochemical and endocrinological lines of investigation yielding important results. In 1935, Kutscher and Wolbergs<sup>1</sup> described the occurrence in high concentration of an "acid" phosphatase in normal human prostatic tissue. The following year Gutman, Sproul and Gutman<sup>2</sup> demonstrated that metastatic prostatic carcinoma tissue in the bones had a high "acid" phosphatase content. Subsequently it was shown by the Gutmans<sup>3,4,5</sup> that the level of the serum "acid" phosphatase activity was specifically increased in patients with metastasizing carcinoma of the prostate.

In 1941, an advance in the management of prostatic carcinoma was made by Huggins<sup>6,7</sup> who described a fall in elevated serum "acid" phosphatase values and clinical improvement in patients with this disease following castration. This procedure was widely adopted, and early reports were universally hopeful. Patients who were followed over a period of a few months experienced cessation of bone pain and a gain in weight. Decrease in prostatic size, softening of hard prostatic nodules, x-ray evidence of regression of metastatic lesions and fall of the serum "acid" phosphatase levels to normal were noted.<sup>8,9,10</sup> When longer follow-ups became available, however, it was apparent that orchiectomy did not cure prostatic carcinoma, but was merely a

palliative procedure, metastases recurring usually after a symptom-free period of six to twenty-four months.<sup>11,12,13</sup> For example, Nesbit and Cummings,<sup>14</sup> in 1942, reported on seventy-five cases followed for at least six months, of whom fifty-five had had good responses to orchiectomy. These authors described the same group of patients two years later<sup>15</sup> and indicated that twenty-one of the fifty-five apparently successful cases had had recurrences, and several had died. Similarly, Bumpus, Massey and Nation<sup>16</sup> reported immediate relief in most cases following orchiectomy but 49 per cent recurrences in one year.

Administration of estrogens alone was first recommended by Herbst,<sup>17</sup> and since has been advocated either as adequate therapy without orchiectomy or as adjunctive therapy to be given after orchiectomy, either routinely or when metastases reappear.<sup>18,19,20</sup>

The following case report describes a study of a patient with carcinoma of the prostate gland over a five-year period of hospitalization, and is presented because it offers an opportunity for correlation of the clinical course, x-ray findings and laboratory data.

#### CASE REPORT

D. G., a seventy year old Jewish man, was admitted to Goldwater Memorial Hospital on September 6, 1940, at the age of sixty-five, with a chief complaint of pain in the joints for two

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years. The patient had been well and pursuing his occupation as tailor until 1938 when, at the age of sixty-three, he began to have pains at first in his hips, and later in his knees, elbows, shoulders and wrists. In 1939, he was admitted to another hospital where a diagnosis of osteoarthritis was made and physiotherapy was prescribed. He was transferred to Goldwater Memorial Hospital for further care on September 6, 1940. His past health, except for a hemorrhoidectomy and a right cataract extraction had been good. The system review was negative except for some nocturia for the past year.

mm. and hemoglobin 90 per cent (Sahli). The erythrocyte sedimentation rate was 64 mm. in one hour (Westergren). The blood urea nitrogen was 16.0 mg. per cent and the fasting blood sugar 88 mg. per cent. The urine was acid with a specific gravity of 1.020, contained no detectable albumin or sugar and had a normal sediment. The blood Wassermann test was negative. Electrocardiography revealed only a left axis deviation. X-ray studies of the knees, hips, spine and hands revealed findings compatible with the diagnosis of rheumatoid arthritis and osteoarthritis. At this time there were no lesions in

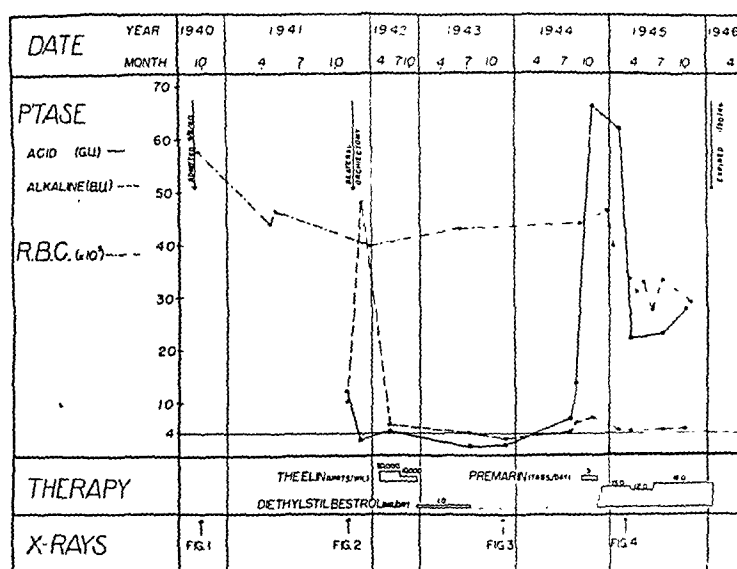


CHART. Course in the hospital."

Physical examination on admission revealed the patient to be an elderly man whose chief findings consisted of flexion deformities of the knees, with swelling and limitation of motion of the knees, ankles, hips, elbows and wrists. The head revealed a right aphakia and a left cataract. The neck was not abnormal. The lungs were normal to percussion and auscultation. The heart was normal in size and showed regular rhythm and a rate of 80. The heart sounds were of poor quality and there was a soft apical systolic murmur. The blood pressure was 150 mm. of mercury systolic and 70 mm. diastolic. The abdomen showed no abnormality. The prostate was described as "firm, nodular, non-tender."

The complete blood count was normal, with red blood cells numbering 5.8 millions per cu.

the bones which could be interpreted as those resembling metastases. (Fig. 1.)

The admission diagnoses were: (1) Rheumatoid arthritis and osteoarthritis; (2) benign prostatic hypertrophy.

In 1940, the patient was given salicylates for pain and whirlpool baths for his legs. He was confined to bed, but was afebrile and fairly comfortable.

In 1941, the treatment was continued as before, and during the first few months of the year he was gradually allowed up in a wheelchair. In September, however, he stated that for the past few months his peripheral joint pain had gradually grown worse. He also complained of pain in the spine, and it was most severe in the hips. His nocturia had continued, and now he also complained of frequency, burning on

urination and occasional dribbling. He had been feeling poorly and his appetite had decreased. Physical examination at this time revealed tenderness over the sternum, costal margins, spinal column and sacrum. Rectal examination revealed the prostate to be "enlarged to the size of a small apple, tender, stony-hard and coarsely nodular." His residual urine was found to be 100 cc. The blood urea

enced an increase in appetite and in general had a greater sense of well being. The residual urine and dribbling disappeared and the frequency diminished. On November 28th, the "acid" phosphatase had fallen to 2.9 G.U. per cent and the "alkaline" had risen to 48.2 B.U. per cent. X-rays of the spine and pelvis at this time revealed no change from the previous films. The red blood cell counts during this



FIG. 1. September 26, 1940. The pelvis shows no evidence of metastases.

nitrogen was 35 mg per cent. Examination of the urine revealed no abnormality. X-ray studies at this time revealed diffuse osteolytic and osteoplastic lesions throughout the pelvis and upper femora (Fig. 1), the dorsal and lumbar spine and the ribs. These findings strongly suggested generalized metastases. Phosphatase determinations at this time revealed values for "acid" phosphatase of 12.6 Gutman units and of 10.1 Bodansky units for "alkaline" phosphatase. A diagnosis of carcinoma of the prostate gland with widespread metastases was made.

On November 13th, a bilateral orchiectomy was performed. Over the next month the patient's pain diminished markedly and he experi-

year were around 4.5 million per cu. mm. with hemoglobin concentrations around 90 per cent. His further progress is indicated on the accompanying chart.

During 1942 the patient was free of pain (except for peripheral joint pain due to his arthritis) and was up in a wheel chair. In February, rectal examination revealed the prostate to be "about half the size it was before operation and much softer in consistency." At this time the findings on x-ray films of the bony pelvis were still unchanged. From March to July the patient received 10,000 U. of theelin by injection twice weekly and from July to December 10,000 U. were given once weekly.

In December, he was placed on 1 mg. of diethylstilbestrol a day by mouth. In May, the "acid" phosphatase was 4.3 G.U. per cent and the "alkaline" 5.9 B.U. per cent. X-ray studies in December showed bone regeneration in the pelvis and lumbar spine and no evidence of metastases in the ribs or dorsal spine.

During 1943 the patient's only complaints were referable to his peripheral joints and he

pelvis showed considerable bone regeneration and in November (Fig. 3) there was disappearance of all the bone changes which had resulted from metastatic foci. Rectal examination, however, at this time revealed an "enlarged, hard prostate."

The patient continued well throughout 1944. In July, however, when the patient's only symptom was joint pain, the "acid" phosphatase

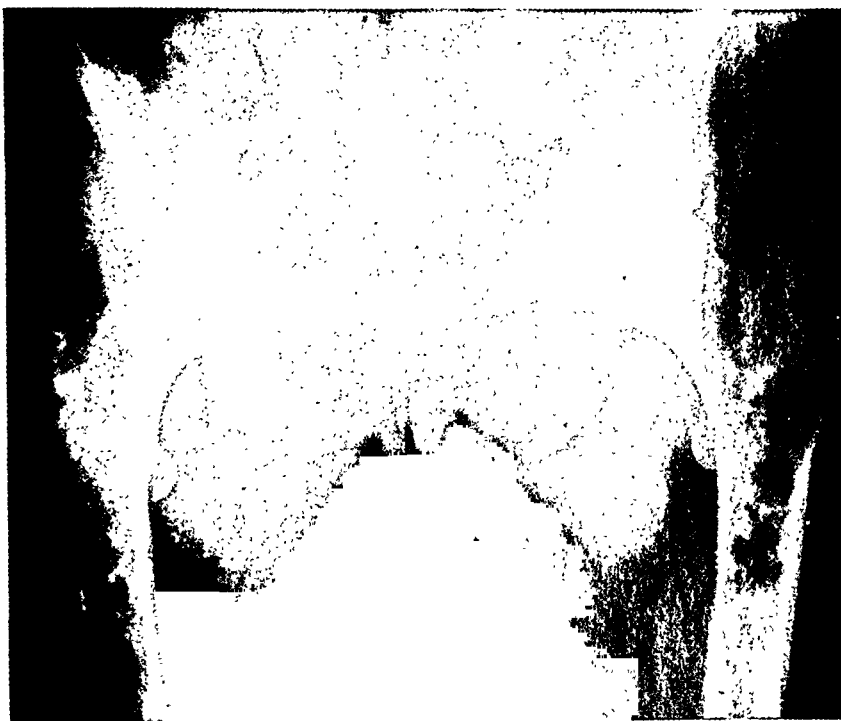


FIG. 2. October 23, 1941. There are diffuse osteolytic and osteoplastic lesions throughout the pelvis, upper femora and lumbar vertebrae. These findings are strongly suggestive of generalized metastases.

required only salicylates for pain. Subjectively he was relatively well. The red blood count was 4.3 million per cu. mm. with a hemoglobin concentration of 85 per cent. The urine showed a trace of albumin and many leukocytes in the sediment, but was otherwise normal. The blood urea nitrogen was 21.6 and 17.6 mg. per cent on two determinations. The erythrocyte sedimentation rates were 51 and 71 mm. in one hour on two occasions. From January until July he received 1 mg. of diethylstilbestrol a day by mouth. In July, the "acid" phosphatase was 1.9 G.U. per cent and the "alkaline" 4.0 B.U. per cent and in December these values were 2.2 G.U. per cent and 3.0 B.U. per cent, respectively. In July, x-rays of the spine and

was found to be 7.1 G.U. per cent and the "alkaline" 4.4 B.U. per cent. One month later these values were 13.7 G.U. per cent and 6.3 B.U. per cent, respectively. Rectal examination at this time revealed that the prostate was "normal sized, nodular, irregular, firm." X-rays of the pelvis revealed no evidence of metastases, but there was a small area of decalcification in the neck of the right femur which could be interpreted as a metastatic lesion. The patient was given a natural conjugated estrogen (Premarin). On October 17th, the "acid" phosphatase was found to be 66.3 G.U. per cent and the "alkaline" 7.2 B.U. per cent. There was a female pubic hair line, but no hypertrophy of the breast tissue, and it was decided



to give large doses of estrogenic substances. Accordingly, the patient was placed on diethylstilbestrol 5 mg. three times a day by mouth. Rectal examination revealed a "flat, firm, nodular prostate." His red blood cell counts during 1944 were around 4.4 million per cu. mm. and hemoglobin concentrations averaged 90 per cent. The urine continued to show a trace of albumin with many leukocytes and

findings were unchanged and the blood urea nitrogen was 13.9 and 17.7 mg. per cent on two occasions. The erythrocyte sedimentation rate was in the range of 73 to 102 mm. in one hour in six determinations. One Gm. of ferrous sulfate a day was given without appreciable effect. The "acid" phosphatase in January was 62.2 G.U. per cent and the "alkaline" 4.8 B.U. per cent. On 15 mg. of stilbestrol a day the patient



FIG. 3. November 17, 1943. The pelvis and upper ends of the femora show considerable bone regeneration. There are no metastases to the vertebrae.

occasional erythrocytes in the sediment. The blood urea nitrogen was 18.3 mg. per cent, and the erythrocyte sedimentation rate was 68 mm. in one hour.

The patient was subjectively well until the middle of 1945, when he began to experience progressive increase in pain in the back, pelvis and hips which required 60 mg. of codeine subcutaneously every six hours. He was unable to carry on wheelchair activity and he became progressively weaker and paler. His appetite began to fail. The red blood cell counts were in the range of 3.3 million per cu. mm. with hemoglobin concentrations of around 70 per cent. Twice the red count fell below 3.0 million to 2.9 and 2.7 million per cu. mm. The urinary

had shown enlargement of the breasts with pigmentation and enlargement of the nipples and areolae. The female pubic hairline persisted. In February, x-rays of the spine and pelvis showed reappearance of osteoplastic metastatic lesions. (Fig. 4.) In March, because of gastrointestinal intolerance the dose of stilbestrol was temporarily decreased to 12 mg. a day. At this time the "acid" phosphatase was found to have fallen to 22.4 G.U. per cent with 4.4 B.U. per cent for the "alkaline" phosphatase. Because of this fall the dose of stilbestrol was increased to 16 mg. a day which was supplemented with 4 cc. of aluminum hydroxide gel and was tolerated by the patient. However, no change in the patient's downward course oc-

curred, and in July and October the "acid" phosphatase values were 23.3 and 27.7 G.U. per cent, respectively. The corresponding "alkaline" phosphatase values for these determinations were 4.9 and 5.0 B.U. per cent. Rectal examination in August showed a "slightly enlarged, fixed, irregular, firm prostate." In October, x-rays showed evidence of osteoplastic

entire body. There was a fracture of the right humerus (postmortem).

*Gross examination* showed that the head was not unusual. The brain was not removed. The breasts were prominent, and the areoli were deeply pigmented. Much fat and glandular tissue was noted in the breasts, and on cut section, a small amount of creamy white liquid exuded.



FIG. 4. February 28, 1945. The lumbar spine and pelvis show osteoplastic metastatic lesions.

metastases in the ribs with a pathological fracture of the seventh rib on the right side.

In 1946 the patient was very feeble and markedly emaciated. He ate poorly and had continuous pain requiring 60 mg. of codeine every six hours. He expired on January 20th. In the postmortem handling of the body a fracture of the right humerus occurred.

The final clinical diagnoses were: (1) Carcinoma of the prostate gland with generalized metastases to the bones; (2) rheumatoid arthritis and osteoarthritis.

A postmortem examination was performed twenty-four hours after death. The body was that of a poorly nourished, poorly developed white male with marked evidence of recent weight loss. There was marked pallor of the

The lungs were emphysematous and somewhat congested. The heart was small and weighed 200 Gm. The myocardium was dark brownish-black in color. The endocardium was slightly thickened, and the valves presented some slight calcific changes in the rings. The coronary arteries showed sclerosis, but were patent. The aorta presented numerous intimal ulcerations, with thrombus formation especially in the abdominal portion. The gastro-intestinal tract presented no abnormalities. The liver weighed 1,100 Gm. It was dark brown and on cut section presented a homogenous smooth surface, on which the lobulations were markedly increased. There were many small dark blue mottled areas. In the head of the pancreas there was a firm, granular fibrotic, grayish area. The rest of the

pancreas was normal. The spleen was small, pink-violet in color and firm. The left kidney was larger than the right and weighed 150 Gm. The architecture was normal. The right kidney was small, weighing 50 Gm. The surface was smooth. On cut section the cortex was almost completely absent, and there was poor demarcation of the medulla. The right renal artery was completely occluded at its origin by a well organized thrombus, which extended from an old thrombus of the aorta. The adrenals were normal in size and on cut section. The urinary bladder was small, contracted, and thickwalled, with numerous submucosal hemorrhages. An occasional small cystic area was noted in the mucosa. The prostate was small but very firm. The external surface was irregular. On cut section it presented a moderately firm, homogeneous, grayish-white surface with numerous small yellowish-white, stony hard nodules. Section through several vertebrae showed a pale and friable marrow. The penis was normal. There were scars in the scrotum which represented the incision for the old bilateral orchiectomy. The extremities revealed only pallor of the nailbeds.

*Microscopically*, the left lower and right lower lobes of the lungs revealed dilated alveoli, anthracotic pigment and congestion. In the liver there was a marked deposition of hemosiderin both intra- and extracellularly. Small patchy areas of fatty degeneration and atrophy with fibrous tissue replacement were noted. Special stain showed hemosiderosis. There was much diffuse hyperplastic sclerosis of the Malpighian arteries of the spleen, with hemosiderosis. Sections through the pancreatic head showed marked hyalinization and fibrosis of the islet cells and acini, with fibrosis and tissue replacement. A large portion of tissue could not be evaluated because of postmortem tissue degeneration. The larger vessels showed varying degrees of sclerosis. One artery showed marked hyperplastic intimal thickening with almost complete obliteration of its lumen. The left kidney showed an increase in the number of the glomeruli but the architecture was otherwise normal. The small arteries showed mild thickening of the walls. The afferent arterioles also showed moderate thickening of the walls. The

right kidney showed generalized atrophy, with hyalinization of the glomeruli, and interstitial fibrosis. Many hyaline casts were present in the collecting tubules. The larger arteries showed advanced arteriosclerosis with marked diminution of their lumina. Areas of old infarctions with fibrosis were seen. Localized collections of lymphocytes were seen in the interstitial tissue. Sections through the prostate showed the presence of large numbers of irregular acini, as well as individual collections of cells arranged in cords. These cells were irregular in outline and were hyperchromatic. They showed rapid proliferation and invasion into adjacent structures. The bladder mucosa was infiltrated with a considerable number of inflammatory cells, mostly lymphocytes and plasma cells. In areas the mucosa was seen to dip downward, forming gland-like spaces. Large, irregular, hyperchromatic prostatic cells were seen to invade the bladder wall. The breasts showed some hyperplasia of the glandular elements with some dilatation of the ducts. An amorphous pink staining material was noted in the ducts. Section through the bone showed the bony trabeculae to be partly broken up in areas, and the marrow, which was fibrous, was infiltrated by large masses of cells. These had an irregular acinar arrangement but frequently showed disruption of the basement membranes. The component cells had small dark nuclei which varied considerably in size and staining characteristics and had abundant eosinophilic cytoplasm. No osteoblastic increase was noted. The process consisted primarily of bone destruction rather than new bone formation.

*The final pathological diagnoses were:* (1) Adenocarcinoma of the prostate with metastases to bone and bladder wall; (2) hypertrophy of glandular elements of the breasts (due to estrogenic therapy); (3) absence of testes (previous operative removal); (4) chronic cystitis, and (5) atrophy of the right kidney due to arterial obstruction by an old thrombus.

#### COMMENT

This patient's course was similar to that of most patients with prostatic carcinoma who are diagnosed after metastases have

occurred and who are then subjected to orchiectomy. In this instance, however, the velocity of the disease seems to have been slower, the course lasting four years and three months from time of definite diagnosis until the time of death. Also, the symptom-free period following orchiectomy in this patient was over three years, which is a longer time than usually elapses.

Although the pain in this patient was frequently difficult to evaluate because of the coexistence of arthritis, it was apparent that he had had marked and prompt relief of his bone pain following orchiectomy. It was believed that during the years 1942, 1943, 1944 and the first half of 1945, what pain he experienced was in the peripheral joints and was due to arthritis and not metastases. His prostate became smaller following orchiectomy, and its consistency became somewhat softer. On admission this patient was thought to have benign prostatic hypertrophy. However, in view of the slow course of the malignancy it seems possible that the prostate even then was carcinomatous. The *x*-ray findings in this patient changed in the expected fashion in response to orchiectomy, but it took two full years for complete disappearance of the abnormalities due to metastases. It is interesting to note that the primary lesion remained small after orchiectomy even though extensive metastases to the bones had reappeared, and at autopsy the prostate gland was found to be small.

The typical changes to be expected in the phosphatase values following orchiectomy were described in detail by Sullivan and the Gutmans.<sup>5</sup> Our patient showed similar changes. An important point in our case is that the "acid" phosphatase was the first index to recurrence of widespread dissemination of the carcinoma, rising to 7.1, 13.7 and 66.3 G.U. per cent in July to October, 1944. Subjective symptoms did not appear, however, until the middle of 1945. Also

*x*-rays taken at the time of the rise in "acid" phosphatase showed only one area of decalcification which could be metastatic, and it was not until a few months later that generalized metastases appeared in the *x*-ray films.

Estrogens were used in this case first in small doses as routine postoperative therapy. In 1943, when the patient had shown restitution of bony architecture to normal, and the clinical course was satisfactory, estrogenic therapy was discontinued. Later, when the "acid" phosphatase began to rise, large doses of diethylstilbestrol were given. It may be noted that while on these doses our patient had a fall in "acid" phosphatase from 62.2 to 22.4 G.U. per cent. However, the clinical course was unaffected, and the drop in phosphatase may possibly have represented cellular and biochemical changes in the metastatic tissue rendering it less able to elaborate "acid" phosphatase as the patient approached a terminal state. The microscopic changes in breast tissue due to diethylstilbestrol have been described<sup>21</sup> and the changes found in our patient were similar.

The reason for exacerbation of prostatic carcinoma after clinical remission due to orchiectomy is not clear. Increased androgenic activity of the adrenal cortex has been postulated. Herbst<sup>22</sup> reported a series of cases in which the patients were treated with estrogens, of whom four had post-mortem examination of the adrenals. Of these, one showed hypertrophied adrenals. In a report of a case, Gilbert and Margoles<sup>23</sup> found the adrenals to be normal. In our patient the adrenals appeared grossly normal, but unfortunately no histological sections were available.

#### SUMMARY

1. A case of carcinoma of the prostate gland with metastases to the bones is presented because of the opportunity to study

over a prolonged period of time the correlation of clinical course, laboratory findings and x-ray with orchiectomy and administration of estrogens.

2. Orchiectomy was an effective palliative procedure. Following it, there was cessation of bone pain, improvement in appetite and increased sense of well being. The prostate became smaller and softer, bone metastases disappeared and elevated serum "acid" phosphatase values became normal.

3. Symptoms and x-ray and chemical signs of widespread metastases reappeared, however, after a period of more than three years.

4. Diethylstilbestrol was administered in large doses after signs of recurrence of metastases appeared. While receiving this drug, the patient was comfortable for several months before he began a final downhill course.

5. The serum "acid" phosphatase determination was an accurate and sensitive index to the existence of metastases from prostatic carcinoma.

We wish to express our gratitude to Dr. Henry K. Taylor who read and interpreted the x-ray findings.

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# Renal Damage Resulting from Idiosyncrasy to Neoarsphenamine\*

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SEVERE renal damage is a relatively rare complication of arsenical therapy. Stokes,<sup>1</sup> in regard to renal injury, states "This complication of the use of the arsenicals may be asserted to occur, for all practical purposes, only as the result of the administration of toxic doses or preparations." Likewise, Moore<sup>2</sup> states "There is, so far as we know, no adequate evidence that . . . the arsenical preparations . . . , given in average therapeutic dosage, will cause renal damage even in an already diseased kidney, except in association with other evidences of grave drug intoxication such as dermatitis, blood dyscrasias, severe stomatitis or enteritis." "All these renal reactions are fortunately very rare. In actual practice renal damage from the arsphenamines need not be feared." Acid arsphenamine has been found repeatedly to cause a severe hemorrhagic nephritis, but alkalinized arsphenamine rarely produces severe kidney damage.

Two patients with death resulting from renal damage due to mapharsen were reported during a six-year period, 1935 to 1942.<sup>3</sup> Another fatality from nephritis, which was attributed to mapharsen, was reported in 1944.<sup>4</sup> In an analysis of the results of triweekly mapharsen therapy, Eagle<sup>5</sup> found only four instances of severe renal damage occurring in 4,823 patients with the condition. Severe kidney injury as a result of arsphenamine is very rare.<sup>6</sup> Neoarsphenamine has been found to cause renal damage.<sup>7</sup> During a seventeen-year

period, 1,355,058 doses of neoarsphenamine were administered in the Navy, with two fatal and five other severe renal reactions.<sup>8</sup> Four of these cases clinically simulated acute glomerulonephritis, with hematuria, albuminuria, anuria, azotemia and hypertension. In the others no hematuria or hypertension were present but instead a picture of acute nephrosis developed.

Experimental injections of massive doses of arsphenamine and neoarsphenamine in rats have been found to cause severe nephritis and usually death.<sup>9</sup> Therapeutic dosages, however, result in only very slight renal impairment. A few casts and a trace of albumin are not uncommon on the day following an arsenical injection, and the blood urea nitrogen value may be slightly increased. Elliott and Todd<sup>10</sup> studied renal function by measuring phenolsulfonphthalein excretion and the blood urea nitrogen level in a group of patients before and after arsphenamine injections. A slight reduction in renal function was noted in some cases after therapy. McFarland,<sup>11</sup> in a study of the effects of antiluetic therapy on the normal and diseased kidneys, found that arsphenamine causes only slight renal irritation and that neoarsphenamine appears to cause less reaction than arsphenamine.

Because of the rarity of renal damage as a result of neoarsphenamine therapy, and because recovery occurred following such an unusually severe reaction, it is thought worth while to report in some detail the following case history.

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## CASE REPORT

M. N., a white female thirty-nine years of age, who had been known to have syphilis for eleven years, was found to have character changes and lapses of memory in 1944. She also complained of "lightning pains" in her legs at that time. In the summer of 1944, she received a course of malarial fever therapy, followed by ten mapharsen injections at weekly intervals. This was, in turn, followed by eleven bismuth injections during the winter of 1944 and 1945. During the course of malarial treatment in 1944, several blood urea nitrogen determinations were made as well as a number of routine urine examinations, all of which were normal. She complained of no urinary symptoms, such as burning or frequency. A phenolsulfonphthalein test in June, 1944, revealed 25 per cent excretion of the dye in thirty minutes and a total of 50 per cent excretion in sixty minutes.

On February 13, 1945, the patient received 0.1 Gm. neoarsphenamine intravenously without any untoward effect. This was, as far as can be determined, her first treatment with this drug. Subsequently, the patient did not return to the clinic for about six months.

In October, 1945, the patient began again to have frequent "lightning pains" in her legs. On October 18th, she received 0.2 Gm. neoarsphenamine intravenously. Within a few hours nausea and vomiting appeared. After six hours a purpuric rash appeared over her face and neck. A tourniquet test (Rumpel-Leede) the following day was normal. Intractable vomiting, loss of strength, weight loss, hematemesis and epistaxes developed and continued until the time of her hospital admission on October 26, 1945. The skin rash disappeared after three or four days, but at the time of admission, eight days after the injection of neoarsphenamine, she had the additional complaints of diarrhea and constant hiccupping.

The patients' blood pressure on admission was 115/80, the pulse was 80, the temperature was 98.0°F. and the respirations were 22 per minute. The patient showed evidences of recent vomiting. Singultus was present. She was somewhat confused and her speech was thick and slurred. Her skin was very dry and there was

evidence of marked loss of weight. There was pallor of the skin but no evidence of jaundice or rash was found. The tourniquet test (Rumpel-Leede) for capillary fragility again showed a negative reaction. A few small submaxillary, axillary and inguinal nodes were felt. The pupils reacted to accommodation but not light. Extra-ocular movements were normal. The fundi were normal. The nose and mouth were coated with dried, clotted blood. Examination of the heart and lungs revealed normal findings. There were no palpable abdominal masses. Some generalized abdominal tenderness was noted. Examination of the pelvic organs and rectum was negative. Neurologic examination revealed a coarse tremor of the outstretched hands, generalized weakness and diminished vibratory, position and pain sensation in the lower extremities. The patellar and achilles reflexes were absent, and no Babinski sign could be elicited.

The hemoglobin was 8.0 Gm. per cent. The volume of packed red blood cells was 30 cc. per cent. The icteric index was 4. Platelets were 400,000 per c.mm. (Rees-Ecker method). The white blood count was 8,400 per c.mm., with 7 per cent juveniles, 71 per cent neutrophils, 1 per cent eosinophils, 20 per cent lymphocytes and 1 per cent monocytes. The blood Kahn reaction was reported as doubtful. The spinal fluid which contained 5 lymphocytes per c.mm. showed a positive Kahn reaction and a colloidal gold curve which was 555555554. Urine examination revealed albumin (two plus) and two white blood cells per high power field in the centrifuged specimen. The urine was scanty, only 4 cc. being obtained in eight hours. The blood urea nitrogen level was 193 mg. per cent. Additional blood chemical data are presented in the accompanying table. Stool examination revealed no gross blood, and no pathogens were found in a culture of the stool. A phenolsulfonphthalein excretion test revealed no trace of dye after two hours.

Treatment at the hospital consisted of parenteral administration of large quantities of 5 and 10 per cent glucose solutions and plasma. The patient developed a diffuse, soft edema and her pallor became more pronounced. Nausea and vomiting continued unabated for seven

## LABORATORY DATA

Date	Cc. Per cent Hemato- crit	W.B.C.	Blood Urea Nitrogen Mg. Per Cent	Vol. Per Cent CO <sub>2</sub> Combining Power	Albumin Gm. Per Cent	Globulin Gm. Per Cent	Chloride Mg. Per Cent	Calcium Mg. Per Cent	Phos- phorus Mg. Per Cent
10/26/45	31	8,400							
10/29/45	27.5	15,700	193		3.2	1.6			
10/31/45			200	25					
11/1/45				22			610	9.9	8.2
11/5/45	25.5	9,000	212	28					
11/7/45	24.0	9,700							
11/9/45			156		4.6	1.7			
11/13/45			92				610		
11/15/45	22.0	5,700	63	44					
11/20/45			41	44	4.6	1.5			5.5
11/24/45	23.0	5,100							
11/26/45			41						
12/7/45			33	23					
1/4/46			16.5						

days and then ceased abruptly. At that time the blood urea nitrogen was over 200 mg. per cent and the phenolsulfonphthalein test again revealed no excretion. Oliguria of from 600 to 800 cc. of urine per day persisted for a week, after which time the urine volume increased rather suddenly. On November 3rd (nine days after admission), the patient was able to eat and drink without vomiting. She then began to show gradual improvement. The pulse rate remained normal and she was afebrile throughout her hospital stay. The blood pressure remained within normal limits. On November 9th, the blood urea nitrogen was 156 mg. per cent, on November 13th, 92 mg. per cent and on November 20th, 41 mg. per cent. The carbon dioxide combining power gradually rose from 22 volumes per cent on November 1st to 44 volumes per cent on November 20th. The serum albumin rose from 3.2 Gm. per cent on October 29th to 4.6 Gm. per cent on November 10th. However, the volume of packed red blood cells gradually declined until on November 24th, it was 23 cc. per cent. At that time she had a hypochromic, microcytic type of anemia.

Marked albuminuria was present for six days following admission. The albumin content then diminished, so that after the eighteenth hospital day no further albuminuria was noticed. Leukocytes were numerous in most samples of urine during her hospital stay but only rare

erythrocytes or casts were seen. A urine culture was positive for *Escherichia coli* on November 16th, having previously been negative. Methenamine therapy was instituted and continued until discharge. At this time, thirty-two days following admission, the urine was normal. Phenolsulfonphthalein excretion was 10 per cent in fifteen minutes, 18 per cent total in thirty minutes and 25 per cent total in sixty minutes. The maximum concentration of the urine was 1.018 (specific gravity).

On December 7, 1945, seven days after discharge, the patient complained of slight weakness but was improving generally. The blood urea nitrogen now was 33 mg. per cent and the carbon dioxide combining power was 23 volumes per cent. The urine showed two plus albumin, 3 to 5 hyaline casts, 3 to 5 leukocytes and no erythrocytes per high power field of centrifuged urine.

On January 4, 1946, one month later, the patient had no complaints. The blood pressure was 110/80. The blood urea nitrogen was 16.5 mg. per cent. The urine showed a trace of albumin, a specific gravity of 1.015, no casts, no erythrocytes and ten leukocytes per high power field, after centrifugation.

On June 6, 1946, the patient was found to be feeling very well, was working and had no specific complaints. She was given an injection of 0.1 Gm. of bismarsen, which was followed by



nausea, vomiting, hematemesis and diarrhea for one week. However, there were no symptoms of urinary tract involvement during this episode.

The patient was last seen on June 26, 1946. At this time she had no complaints. She had no urinary tract symptoms of any kind. The urine at this time showed no albumin, no erythrocytes, no casts, and 3 to 5 leukocytes per high power field of the centrifuged specimen. The phenol-sulfonphthalein test revealed 35 per cent excretion of the dye in thirty minutes and 50 per cent total in fifty minutes. Urine culture revealed *Escherichia coli* to be present. The total renal plasma flow, as measured by the paraminohippurate method,<sup>12</sup> was 225 cc. per minute per 1.73 sq. meters (Normal range: 491 to 695). Glomerular filtration according to the mannitol clearance test,<sup>13</sup> was 55.9 cc. per minute per 1.73 sq. meters (Normal range: 101 to 133).<sup>14</sup> Thus, the renal function was impaired to a moderate extent seven months after the acute episode.

#### COMMENTS

Because of an idiosyncrasy to neoarsphenamine the subject of this report appears to have developed purpura, a severe gastrointestinal reaction and severe renal damage which seemed to be primarily tubular in character. Through a previous injection of this drug, the patient probably developed sensitivity, which became manifest after the second injection eight months later. The amount of neoarsphenamine given was small enough to exclude direct toxic injury of kidney parenchyma.

Sensitivity reactions to neoarsphenamine and to other trivalent arsenicals are not uncommon, but the sensitivity is usually manifested only by the development of a skin eruption. Renal sensitivity reactions may be either mild or severe. There may be slight albuminuria, cylinduria and hematuria which disappear after a few hours or days. The picture of acute glomerulonephritis with anuria, hematuria, albuminuria, azotemia and hypertension may be seen or,

as in this case, a picture of nephrosis may be encountered. Chemical nephrosis, due to bichloride of mercury, is characterized by degeneration and necrosis of the cells lining the convoluted tubules. Similar lesions have been described as a result of sensitivity to sulfonamides.<sup>15</sup> In the latter instances small doses of sulfonamides have produced the nephrotic syndrome and crystalluria has been absent in such cases. Anatomically, these lesions have been found to consist of thrombi in the interlobar arterioles and veins accompanied by evidence of tubular degeneration. The clinical picture in such cases is similar to that of chemical nephrosis in which azotemia, edema, oliguria, albuminuria and hyposthenuria are found while hypertension does not occur. In the present case, however, glomerular residual damage is indicated by the impaired mannitol clearance.

Because of the gastrointestinal symptoms which developed following a bismarsen injection six months after the severe neoarsphenamine reaction, it appears likely that the patient described here is hypersensitive to all trivalent arsenicals. Sensitivity to one arsenical denotes probable sensitivity to other arsenical preparations in most instances.<sup>6</sup>

#### SUMMARY

1. A review of the available literature reveals the relative infrequency of severe renal reactions following arsenical therapy.

2. A case is presented of severe nephrosis accompanied by purpura and gastrointestinal reaction which followed the administration of a small dose of neoarsphenamine.

3. Despite the severity of the reaction nearly complete recovery has occurred in this case.

4. The renal injury in this instance is thought to have been due to a sensitivity reaction. Clinically, the manifestations were similar to those of nephrosis caused by

bichloride of mercury and accompanying sulfonamide sensitivity.

I wish to thank Dr. B. V. Jager and Dr. M. M. Wintrobe for their advice in the preparation of this report.

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# Aberrant Atrioventricular Conduction in a Patient with Paroxysmal Tachycardia, a Short P-R Interval and a Normal QRS Complex

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THE interesting physiologic aspects concerned with the condition known as aberrant atrioventricular conduction or Wolff-Parkinson-White syndrome<sup>7</sup> has recently led to increasing investigation and reporting of the subject. To explain the observed phenomena, Holzman and Scherf,<sup>2</sup> and almost simultaneously Wolferth and Wood,<sup>6</sup> postulated the existence of an accessory muscle bundle capable of bypassing the normal A-V conduction system and directing the impulse to one ventricle prematurely. Subsequently Wood, Wolferth and Geckler<sup>8</sup> actually demonstrated such a structure in an individual who during life exhibited evidence of Wolff-Parkinson-White syndrome with paroxysms of tachycardia. More recently Rosenbaum et al.,<sup>5</sup> in an exhaustive analysis of the problem stated, among other conclusions, that more than one accessory bundle may be present although not all may be functioning at the same time. It is believed that the impulse reaches the ventricles both by way of the accessory structure and the normal auriculo-ventricular system.

There is little diversity of opinion at present regarding the diagnostic criteria for this condition. These are summarized as follows: (1.) Shortened P-R interval, usually to .10 seconds or less; (2.) widened QRS complex, often .14-.16 seconds. The P-S interval (beginning of P to end of QRS) remains within the normal range; (3.) slurred initial stroke of the QRS complex. Addi-

tionally, there are often extensive degrees of axis deviation, commonly to the left, and individuals with this syndrome are subject to paroxysms of tachycardia. These are ordinarily supraventricular in origin but paroxysmal ventricular tachycardia has also been observed.<sup>3</sup> Auricular tachycardia is thought to occur when an impulse proceeds normally through the A-V node, the bundle of His and its branches but continues to complete a circus by returning to the auricle through the anomalous conductor.

There is some evidence, however, that one of the criteria, namely, abnormal widening of the QRS complex, may not be strictly valid. When the QRS complex normally is very brief, .04-.06 seconds, considerable widening may occur and still leave the total within the normal range. However, in such cases the initial portion of the ventricular complex shows characteristic slurring and the P-R interval is shortened. Fox<sup>1</sup> reported one such case in which the QRS was .08 seconds in duration. He was able to shorten it further by the administration of quinidine and to lengthen it with digitalis and prostigmine. He suggested that only two requirements are needed for the diagnosis of aberrant atrioventricular conduction, namely, a shortened P-R interval and a distorted QRS which may be of normal or lengthened duration.

Recently a case was observed which

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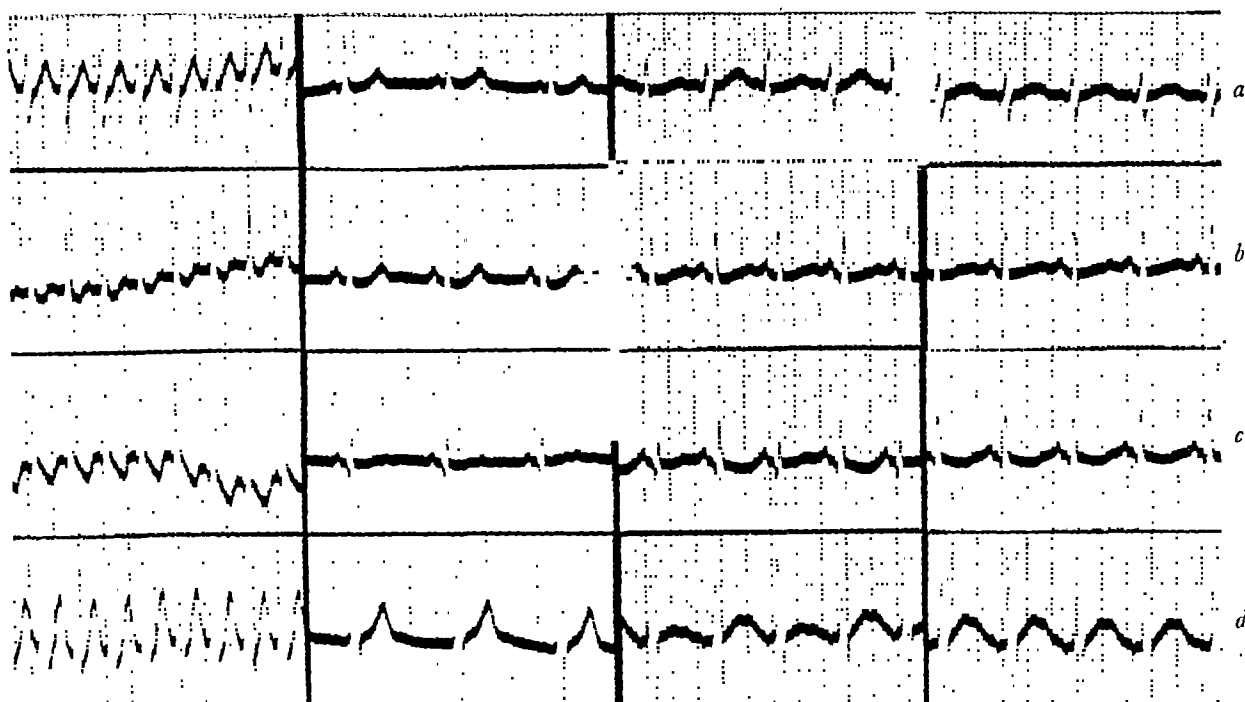


FIG. 1. *a*, Paroxysmal supraventricular tachycardia; *b*, "normal" pattern; *c*, following administration of quinidine; *d*, following administration of quinidine and atropine.

although fulfilling some of the requirements of accessory auriculoventricular conduction is not covered by even these modified criteria.

#### CASE REPORT

An opera singer, thirty-two years of age was admitted for study of attacks of rapid heart action. These had been present for seven years and were moderately disabling. The onset was sudden and unpredictable and the duration varied between a few seconds and several hours. The termination of the attacks was also abrupt and could sometimes be induced by ocular pressure. There were no other cardiac symptoms and the history was not otherwise significant. The physical examination was essentially normal. The heart was not enlarged, the rate was 68 and the rhythm was regular. No murmurs or thrills were noted. X-ray and laboratory studies were all within the normal range.

The electrocardiogram was remarkable only in that the P-R interval was .10 seconds in duration and the QRS .08 seconds. The axis was  $+34^\circ$ , a small  $Q_3$  was noted and the ventricular complex was otherwise undistorted and normal in appearance. It was thought to represent an instance of nodal rhythm. Following rather vigorous physical effort an attack of

tachycardia was noted and recorded. The tachycardia was apparently auricular in origin, the rate was 210 per minute and a marked change in the appearance of the ventricular component was apparent. The axis had rotated  $60^\circ$  to  $+94^\circ$ .

In view of the change in axis noted during the tachycardia and the previously observed short P-R interval the possibility of aberrant A-V conduction was considered. Attempts were made to widen the QRS complex with cholinergic drugs but these were not successful. At this point quinidine was employed in an effort to depress the aberrant conduction pathway and so demonstrate its presence. After preliminary administration of the drug to determine sensitivity the patient was given .6 Gm. of quinidine at intervals of one hour until three doses had been administered. Following the last dose a tracing was made which demonstrated an alternating shift of the axis without change in the P-R:QRS relationship. Every other beat strongly resembled the complexes observed during the paroxysm of tachycardia while the remainder were unchanged except for the overall effects of the drug. The patient was then given 1.0 mg. of atropine intravenously following which the electrocardiogram revealed complete reversion to the form

first noted during the tachycardia. However, the P-R interval remained unchanged to ordinary measurement and the QRS duration was unaltered.

#### COMMENT

Since all of the criteria were not fulfilled and most were merely indicated, this case could hardly be considered a characteristic example of Wolff-Parkinson-White syndrome. On the one hand, features were present which strongly suggested the influence of some type of accessory A-V conduction. The short P-R interval with attacks of paroxysmal tachycardia point to such a mechanism while the varying appearance of the QRS complex is consistent with altered ventricular distribution of the impulse. Further, the depressant action of quinidine on the postulated anomalous conductor was manifest through electrocardiographic changes which were further exaggerated by the use of atropine. On the other hand, the QRS complex was neither prolonged nor significantly deformed and no alteration in the P-R:QRS relationship occurred when the anomalous conductor was depressed and apparently inoperative during the administration of quinidine and atropine.

One would suspect, therefore, that if accessory A-V conduction was responsible for the observed phenomena in this subject, that a more complicated mechanism was at work. A number of reported instances of Wolff-Parkinson-White syndrome indicate the presence of several aberrant conductors apparently acting alternately or in various combinations. Cases No. seven and nine of this author's reported series<sup>4</sup> demonstrated striking changes in the form of the ventricular complex occurring spontaneously or following changes in position. This was thought to result from the varying action of several anomalous pathways. Wood, Wolferth and Geckler<sup>8</sup> in their pathologic description of accessory conduction demonstrated multiple anomalous channels. It is suggested, therefore, that in the patient

under discussion, more than one accessory conductor was present and that they were unequally affected by the drugs employed and during the observed paroxysm of tachycardia.

Although it is apparent that no ready or simple explanation is available for the observed phenomena, it is believed that the subject represents one variant of accessory auriculoventricular conduction. It is, perhaps, remotely related to the syndrome of Wolff, Parkinson and White and may, in an even more attenuated form, be responsible for otherwise unexplained instances of paroxysmal tachycardia in apparently normal individuals.

#### SUMMARY

A case of anomalous atrioventricular conduction is described which does not conform to the usual criteria.

A mechanism is suggested to explain the observed phenomena.

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## The Question of "Spasm" of the Coronary Arteries

PHYSICIANS often postulate "spasm" of the coronary arteries to explain episodes of angina pectoris and other types of cardiac pain. Spasm could result from a direct effect of adrenalin or other chemical circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor impulses. Conclusive evidence for such coronary vasoconstriction is, however, fragmentary and incomplete. A vast literature of laboratory observations has been accumulated, but the results of experimental observation on various animals cannot be transposed to man with assurance; it is well known that even the reverse of phenomena observed in animals may be encountered in man. The rich supply of autonomic fibers to the coronary arteries implies a probable vasomotor function. Nevertheless, Gregg was led to conclude in a recent review<sup>1</sup> that "it would seem most difficult to establish and identify conclusively by experimental means the separate effects of nervous influences upon the myocardium and coronary vessels because the physiological functions of these structures are so intimately related that their individual responses may be secondarily modified, each by the other. . . . Until better instruments and methods are devised and used in conjunction with preparations which are capable of normal physiological responses, our knowledge concerning the normal and abnormal func-

tioning of the coronary circulation will be necessarily limited as well as unavoidably inexact."

Studies in man obviate some of these uncertainties and afford important information. The fact that attacks may be brought on by exposure to cold or "by any disturbance of mind"<sup>2</sup> is difficult to explain solely on the basis of long standing intrinsic arteriosclerotic changes in the coronary arteries. Some episodes, particularly those occurring in the absence of effort or increased cardiac work, are best understood as the expression of vasoconstriction or absence of vasodilatation leading to a relatively insufficient coronary blood flow. Relatively recent observations in patients with angina pectoris afford strong evidence of the existence and significance of vasomotor influences. Gilbert, Fenn and Leroy<sup>3,4</sup> observed that patients while breathing 10 per cent oxygen developed pain much more frequently following meals. The increased susceptibility to angina pectoris following meals was abolished by the use of atropine. This evidence, while not conclusive because of possible lessened abdominal distention and other reactions after atropine, is, however, paralleled by other observations. Thus, Freedberg, Spiegl-

<sup>2</sup> HEBERDEN, W. Some account of a disorder of the breast. *M. Tr. Roy. Coll. Phys.*, 2: 59, 1786.

<sup>3</sup> GILBERT, N. C., FENN, G. K. and LEROY, G. V. The effect of distension of abdominal viscera on the coronary blood flow and on angina pectoris. *J. A. M. A.*, 115: 1962, 1940.

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and Riseman<sup>5</sup> in a study of patients with angina pectoris found that holding an ice cube in one hand markedly reduced the capacity of their subjects to perform exercise without pain. This reaction to localized cold was evidently reflex in nature. Conversely, immersion of the hands and wrists in hot water increased the patients' ability to undertake exercise before developing pain. Various factors such as chilling or warming of the blood, changes in minute volume cardiac output, alterations in blood pressure or cardiac rate were excluded as causative influences.

Other clinical observations are of interest in this connection. In several subjects with angina pectoris, Wilson and Johnston<sup>6</sup> observed pronounced electrocardiographic changes of the type produced by temporary occlusion of a large coronary artery which appeared, disappeared and reappeared without any material increase in heart rate or in blood pressure. The character of the electrocardiographic changes suggested that the change in arterial or arteriolar caliber was local and not general. In two of their patients the typical anginal paroxysms were induced by smoking cigarettes. Whether the coronary arteries were affected by vasomotor influences or were directly affected by nicotine or some other constituent of

cigarette smoke cannot be stated, although it is of interest to note that cigarette smoking produces constriction of the peripheral arterioles both in healthy subjects and in patients with angina pectoris. The amelioration of angina pectoris occasionally witnessed after gallbladder surgery with reversion of electrocardiographic changes toward normal likewise may represent interruption of vasomotor influences.<sup>7</sup>

The existence of vasomotor effects on the coronary circulation in no way invalidates the accepted recognition of the widespread pathological changes of arterial narrowing and occlusion in the hearts of patients with angina pectoris; on the contrary, this evidence supplements our understanding of the nature of cardiac pain and the mechanisms whereby it may be induced. The widespread pathologic lesions in the coronary arteries in patients with cardiac pain afford an adequate basis for the operation of the ischemic theory of pain. They must not, however, be considered the exclusive cause of cardiac pain, but rather as constituting the stage on which various factors may operate. Thus, vasoconstriction or absence of vasodilatation, anemia, tachycardia or the lowered blood pressure of shock may act as precipitating agents in the production of pain in a heart whose circulation is already compromised by arterial obstruction.

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<sup>7</sup> FITZ, HUGH T., JR. and WOLFERTH, C. C. Cardiac improvement following gallbladder surgery. *Ann. Surg.*, 101: 478, 1935.

## Potassium Deficiency in a Case of Lymphosarcoma with the Sprue Syndrome\*

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THE clinical manifestations of the sprue syndrome have been known since the comprehensive and lucid description by Gee in 1888.<sup>16</sup> The steatorrhea which is its most constant feature is usually evidenced by copious, pale, offensive stools containing large amounts of fatty acids, soaps and neutral fat. The profound emaciation which results from long continuance of the trouble is accompanied by muscular wasting and a great variety of symptoms which may arise from specific deficiencies. Tetany, skeletal deformities, edema, night blindness, hemorrhages, skin eruptions, peripheral neuritis and megaloblastic anemia are abnormalities which appear to depend upon defects in the absorption or utilization of calcium, phosphorus, protein or the vitamins. Together with other manifestations of the condition they present a picture of extensive and serious undernutrition. Little attention has been paid to loss of electrolytes other than calcium and phosphorus in this symptom-complex but the possibility that a loss of potassium may occur was suggested by the finding of a low concentration of serum potassium in two patients.<sup>17</sup>

The sprue syndrome has been described under a variety of names which include celiac disease, tropical sprue, non-tropical sprue and idiopathic steatorrhea. There is still difference in opinion as to whether the celiac affection in children is identical with the disease in adults and whether the syndrome developing in the tropics is of a different nature from that arising in other areas. It seems certain that whenever and however the sprue syndrome may arise, the fundamental defect is one of intestinal absorption, and the clinical manifestations, while quantitatively various, have been qualitatively similar at different ages and in different parts of the world. Almost precisely similar symptoms, moreover, have been observed in two groups of conditions in which pathological cause of the absorptive difficulty may be demonstrated. One group represents a short-circuiting of food from the upper to the lower part of the gastrointestinal tract and has been encountered after operations or as a result of carcinoma of the stomach or colon.<sup>3,6,12</sup> A similar abnormality has been produced in dogs by resection of all or part of the small intestine.<sup>11</sup> The other group has included

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cases in which there were anatomic lesions of the intestinal lymphatics, of the mesenteric lymph nodes, or of both. In this group are examples of tuberculosis of the lymph nodes,<sup>21,24,28</sup> abdominal Hodgkin's disease, undiagnosed lymphoma with hyperplasia of the lymph nodes, and a case suspected of being lymphosarcoma because of an abdominal tumor and possible lymphosarcoma of the skin.<sup>13</sup> Several other cases having many points in common must be included in this group. The first of these was reported by Whipple in 1907.<sup>34</sup> A medical missionary from Turkey died of a sprue syndrome. At autopsy it was found that the villi of the small intestines were distended by the accumulation of fat-containing multinucleated giant cells and large, foamy endothelial cells. Somewhat similar cases have since been recorded under a variety of titles including malabsorption of fat,<sup>7</sup> mesenteric chyladenectasis<sup>20,26</sup> fat infiltration of the mesenteric lymph nodes<sup>15</sup> and dilatation of lacteals with enlarged mesenteric nodes.<sup>22</sup> The lesions in these cases are so striking that it has been suggested that the sprue syndrome may always be on the basis of lymphatic block,<sup>22</sup> an hypothesis which has little or no anatomic support in the usual case.

This report is concerned with a patient who, during the period of metabolic study, was thought to have uncomplicated non-tropical sprue, but who developed thereafter clinical evidence of lymphosarcoma, of which she died.

Two features were of particular interest and prompted the study. First, along with the commonly observed clinical changes associated with sprue, she was found to have a very low serum potassium level. Second, in order to obtain any significant clinical improvement it was found necessary to treat her with massive doses of vitamin D as well as with a low fat, low starch diet.

#### CASE REPORT

B. K., a Greek housewife, forty-four years of age, was admitted to the New York Hospital on July 21, 1941, with the complaint of diarrhea for nine months and increasing weakness for six months. She was born in Greece. At the age of sixteen she came to this country to be married. She had seven pregnancies in rapid succession. For eighteen months preceding her illness she helped in the kitchen of her husband's restaurant at work of fatiguing nature to which she was unaccustomed. She ate no breakfast, took only a sketchy lunch while she was working and then went home to prepare for the family an evening meal which she was often too tired to eat. She had no known food idiosyncrasies but never drank much milk. In 1924, she had an appendectomy and tubal ligation at Bellevue Hospital. In 1938, she had a contact dermatitis which lasted for almost a year.

She considered herself well until September, 1940, when she gradually developed diarrhea. At first she had only two to four stools a day, but later six or more. The movements were copious, foul-smelling, frothy, usually light in color but occasionally black. No blood or mucus was noted. Occasionally she felt cramp-like pains in the region of the umbilicus. After about three months she became so weak that she was forced to stop work. Her diarrhea continued but was no longer accompanied by cramps. In January, 1941, she consulted a physician who told her that she was anemic. He gave her one injection of a liver preparation, ten intravenous injections of a medicine containing copper and iron, and pills containing iron and vitamins. In April, 1941, he referred her to a hospital where she stayed for two weeks. While there a blood examination revealed 3,100,000 red blood cells, 6,500 white blood cells and a hemoglobin of 60 per cent. An x-ray of the abdomen revealed in the right lower quadrant a spherical mass containing large amounts of calcium. This was diagnosed as a fibroid. She was found to have an achlorhydria both before and after histamine and was thought to have pernicious anemia. Her hospitalization brought her no apparent improvement. Her weakness increased. The muscles of mastication

became so fatigued that she could chew her food only with great difficulty. At times she could scarcely lift her arms. Blurring of vision and tinnitus became troublesome. She noted also numbness and tingling in the hands and feet. She received five more injections of liver extract and three transfusions. She was again admitted to the hospital on May 27, 1941, at which time her red blood count was 4,700,000 with 78 per cent hemoglobin. She was given two more blood transfusions and continued on liver injections. On July 9, 1941, her hemoglobin level was 80 per cent, red blood cells 4,800,000.

During this entire period she had no nausea or vomiting and her appetite was excellent. Her diarrhea continued uninfluenced by treatment and her weight fell from 155 pounds in September, 1940, to 105 in July, 1941.

Physical examination revealed a well developed, placid, extremely emaciated woman weighing 43.5 kg. The skin was fine, dry and sallow in color. No abnormal pigmentation was noted. The hair was gray. There was no lymphadenopathy. Examination of the head and neck was negative. The eyes were normal. The tongue was not reddened or atrophic. The lungs were normal. The heart showed no abnormalities except for occasional extra-systoles. Pulse was 86, blood pressure 90/70. The abdomen was moderately distended and the abdominal wall was thin. The liver and spleen were not palpable. There was a firm, slightly movable mass about 5 cm. in diameter in the right lower quadrant, which on pelvic examination was found to move with the uterus but was not definitely arising from it. No other masses were felt. There was generalized muscular wasting, and profound generalized muscle weakness, without spasticity. The Chvostek and Trousseau signs were elicited. The tendon reflexes in the arms and legs were all absent except for knee-jerks, which could be elicited with reinforcement. Superficial abdominal and plantar reflexes were normal. Sensory examination showed no abnormalities.

Laboratory data at the time of admission were as follows: Urine normal. Red blood cells 6,600,000/mm.<sup>3</sup>, hemoglobin 12.5 Gm., hematocrit 43 per cent, platelets 120,000, white blood cells 9,300 and Kline negative. The stools

were bulky, gray, semi-formed, foul-smelling with a negative guaiac test for occult blood. At this time a twenty-four-hour specimen of stool contained 23.5 Gm. of fat, amounting to 30.9 per cent of the dry weight of the stool.

Analyses of the blood serum on admission revealed the following values: total protein, 5 Gm./100 cc.; calcium, 4.8 mg./100 cc.; phosphorus, 2.2 mg./100 cc.; potassium, 1.3 mEq/L; sodium, 139.8 mEq/L. Gastric analysis showed no free HCl in the fasting specimen, and a free HCl of 8 thirty minutes after histamine.

The plasma prothrombin was 63 per cent and plasma vitamin A 58 micrograms per 100 cc. The results of oral and intravenous glucose tolerance tests were as follows:

BLOOD SUGAR MG./100 CC.

	Fast- ing	30 min.	1 hr.	2 hr.	3 hr.
Oral.....	69	92	126	107	94
Intravenous.....	64	164	111	64	72

Determination of pancreatic enzyme activity in the duodenal contents after intravenous administration of secretin gave the following results, all within normal limits<sup>1</sup>: volume 3 cc./Kg., highest pH 8.15, highest bicarbonate 94 mEq./liter, diastase 10 units/Kg./60 minutes, trypsin 0.87 units/Kg./60 minutes, lipase 162 units/Kg./60 minutes.

Roentgenographic study of the gastrointestinal tract showed a loss of normal mucosal pattern of the jejunum, with apparent spasticity, irregularities of the mucosa and some puddling of the barium. There was a rounded calcified mass in the right side of the pelvis, interpreted as being a calcified fibromyoma.

At the time of admission the patient appeared gravely ill. Her most prominent symptom was extreme weakness. There was no anemia at this time, but her diarrhea continued. She was treated with a high carbohydrate, high protein, low fat diet, parenteral liver extract and added vitamins A, B, C and D, with calcium lactate and potassium citrate by mouth. During the first few months it was necessary to give her calcium intravenously in order to prevent frank tetany. During the first few weeks after admission she

improved a little in that she was a little stronger and able to move about in bed, but there was little change otherwise. Latent tetany was present all the time and the fatty diarrhea persisted. Of particular interest were the changes in the serum potassium which varied from 1.1 mEq/L to 3.2 mEq/L., the usual level being around 2.2 mEq/L. The loss of fat and nitrogen in the stool continued high, the fat varying from 28.8 to 116 Gm. and the nitrogen from 3.8 to 8.3 Gm. per day.

On November 2, 1941, the administration of 500,000 units of vitamin D daily was begun and on January 8, 1942, the dosage of vitamin D was increased to 4,000,000 units a day.\* During the next three weeks she showed more striking clinical improvement than at any time previously. Associated with diminution of the diarrhea and increased muscular strength was a return of her serum calcium, phosphorus and potassium to normal or nearly normal levels.

She was placed in the Metabolism Ward in January, 1942, and a series of studies carried out which will be reported in detail below. She remained in the hospital much of the time. While on a low fat, high carbohydrate, low starch diet, with 1,000,000 to 4,000,000 units of vitamin D daily she was at her best, in that her stools were only one or two a day, although still bulky, she was free of tetany, and was strong enough to be up and about most of the day. Her stools were frequently examined for occult blood. Occasionally they were guaiac positive, but almost all were normal. Repeated x-ray studies after a barium meal showed the same findings as previously.

In March, 1943, she began to have lower abdominal pains and constipation, and within two weeks developed intestinal obstruction. At operation bilateral pelvic masses were found, and a portion of ileum containing a small mass, thought to be metastatic, was removed. Microscopically, these proved to be lymphosarcoma. She was given x-ray therapy over the abdomen, but went rapidly downhill, became deeply jaundiced and died in May, 1943.

Autopsy examination revealed that there was

\* The vitamin D was given in the form of a concentrated solution of irradiated ergosterol supplied by Dr. C. E. Bills of Mead Johnson and Company.

an extensive lymphosarcoma involving the duodenum, jejunum, ileum, colon, liver, right kidney, adrenals, epicardium, myocardium, pericardium, diaphragm, thyroid, uterus, pancreas, pleura and lymph nodes. The lymph nodes chiefly involved were the para-aortic, mesenteric, tracheobronchial, hypogastric and pelvic groups.

There was a large, firm, gray-white tumor mass in the myocardium, also involving the epicardium. The liver weighed 1,850 Gm. and contained numerous tumor nodules. The small intestine showed very striking changes. Beginning at the pyloric ring, the duodenal wall was thickened. There were large masses projecting into the lumen. The ampulla of Vater was invaded. There was slight dilatation of the pancreatic ducts and a few areas of fat necrosis of the pancreas. Throughout the jejunum and ileum there were similar large tumor masses, involving a total of about one-third of the entire wall. Both adrenals contained large masses of tumor, appearing to involve chiefly the medulla. The lymph nodes in the tracheobronchial, pelvic, hypogastric and mesenteric regions were large, firm and gray-white. The lacteals were not dilated. Microscopically all the tumor nodules examined consisted of anaplastic cells with dark nuclei, abundant cytoplasm, many mitotic figures and some tumor giant cells.

#### METABOLIC STUDIES

These studies were started following the striking improvement in the patient's condition associated with the administration of large doses of vitamin D. At this time the etiology of her steatorrhea was unknown. The extremely low concentrations of potassium in the serum before vitamin D therapy was started were of special interest. Similarly low levels of potassium in the serum had been encountered in another patient with the sprue syndrome<sup>17</sup> and these studies afforded an opportunity to investigate the possibility that the potassium deficiency might be due to excessive loss of potassium in the diarrheal stools.

*Methods.* All diets were weighed and prepared on the metabolism ward. During

a given dietary regimen, two diets of approximately the same composition were devised, and these were given on alternate days. Duplicate diets were prepared simultaneously with the diets served to the patient and these duplicate diets were analyzed for nitrogen, potassium, phosphorus and calcium. The fat and carbohydrate of the diet were calculated from standard food tables. Any medication given is indicated in the following discussion, except for vitamin capsules which were administered daily throughout the study. The approximate daily intake provided by this supplement was: Vitamin A 5,000 USP units, thiamin 1 mg., riboflavin 1.2 mg., nicotinic acid 25 mg., pyridoxine 0.116 mg., pantothenic acid 0.48 mg., ascorbic acid 50 mg., and vitamin D 1,000 I.U.

The urine and stools were collected quantitatively, the stools for each period being separated by the administration of carmine red at the end of the period. The periods were of four to six days each. Blood was taken for analysis at the end of each period. The chemical methods used were: potassium in serum, food, urine and stools, Harrison and Darrow;<sup>18</sup> calcium in serum, Kramer and Tisdall;<sup>23</sup> calcium in urine, Shohl and Pedley;<sup>29</sup> calcium in food and stool, Hawk and Bergeim;<sup>19</sup> phosphorus in serum, food, urine and stools, Fiske and Subbarow;<sup>14</sup> nitrogen in food, urine, stools by the macro-Kjeldahl method. Fat was determined in the dried stool by Soxhlet extraction with ether.

The dietary intake during the various periods is tabulated in Table I. The periods during which the massive doses of vitamin D were given are also shown. During periods 1 and 2, the diet was approximately the same as that given for the preceding three weeks, during which time the patient had shown rapid improvement. This diet was high in protein, low in fat and low in starch. No high-starch vegetables were given, and

the bread was thoroughly toasted to dextrinize the wheat starch. Most of the carbohydrate intake was in the form of sugars. In the next two periods, 3 and 4, no change was

TABLE I  
DAILY DIET AND VITAMIN D INTAKE DURING BALANCE STUDIES

Period	Protein	Fat	Carbo- hydrate	Potas- sium mM Per Day	Phos- phorus	Cal- cium	Vitamin D I.U. Per Day
	Gm. Per Day				Mg. Per Day		
1	115	70	350 <sup>1</sup>	126	2100	1420	2,000,000
2	115	70	350 <sup>1</sup>	126	2100	1420	2,000,000
3	115	70	350 <sup>2</sup>	145	2160	1350	2,000,000
4	115	70	350 <sup>2</sup>	145	2160	1450	2,000,000
5	75	150	340 <sup>2</sup>	60	1850	1410	2,000,000
6	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
7	138	75	440 <sup>1</sup>	140	2320	1410	1,000
8	138	75	440 <sup>1</sup>	140	2320	1410	1,000
9	138	75	440 <sup>1</sup>	140	2320	1410	1,000
10	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
11	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
12	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
13	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
14	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
15	138	75	440 <sup>1</sup>	140	2320	1410	2,000,000
16	138	50	440 <sup>1</sup>	140	2320	1410	2,000,000

<sup>1</sup> Carbohydrate predominantly in form of sugars.

<sup>2</sup> Proportion of starch increased.

made in the protein and fat intake nor in the quantity of carbohydrate in the diet. The type of carbohydrate fed was changed in that more starch was given in the form of starch-containing vegetables, and untoasted bread. During period 5, the fat content of the diet was increased to 150 Gm. and the protein intake reduced to 75 Gm. per day. The potassium content of the diet was thereby also lowered from 145 mM to 60 mM per day. In period 6 the patient was returned to the diet given in periods 1 and 2. The diet was then kept constant but during periods 7, 8 and 9, the vitamin D supplement of 2,000,000 units daily which had been given heretofore was discontinued. This vitamin D supplement was resumed at the beginning of period 10 and given until the end of the study. In period 16, the diet was modified by reduction of the fat intake from 75 to 50 Gm. The results of the electrolyte and nitrogen balances are shown in Table II.

*Results.* The changes in concentration of potassium, phosphorus and calcium in the blood serum during the course of somewhat over a year of study are shown in Figure 1. During the first few weeks of hospitalization, the patient was given calcium salts by mouth and calcium gluconate intravenously. The serum calcium was raised to almost normal values and the symptoms of tetany ceased. The diarrhea and weakness persisted and

symptomatic improvement with increase of muscle strength and lessening of the diarrhea. On the 186th day the first balance period was begun.

The results of the potassium, phosphorus, and calcium balance studies are detailed in Table II and shown graphically in Figures 2, 3 and 4. The height of the column enclosed in the solid line indicates the daily intake of the substance. The vertically

TABLE II  
ELECTROLYTE AND NITROGEN BALANCES

Period	Potassium					Phosphorus					Calcium					Nitrogen			
	In-take	Output		Bal.	Serum mM/L	In-take	Output		Bal.	Serum mg. 100 cc.	In-take	Output		Bal.	Serum mg. 100 cc.	In-take	Output		Bal.
		Stool	Urine				Stool	Urine				Stool	Urine				Stool	Urine	
	mM Per Day					mg. Per Day					mg. Per Day					Gm. Per Day			
1	126	30	78	+18	4.1	2100	933	887	+280	5.7	1420	1440	91	-110	9.2	18.6	3.7	10.0	+4.8
2	126	22	84	+20	4.3	2100	574	1108	+418	5.9	1420	1225	154	+41	9.0	18.6	3.0	10.8	+4.8
3	145	57	82	+6	...	2160	1230	817	+113	...	1350	1410	97	-160	...	18.1	4.7	10.5	+3.0
4	145	59	87	-1	3.3	2160	1410	808	-58	4.7	1350	1500	61	-211	8.3	18.1	5.6	11.1	+1.4
5	60	50	35	-25	2.3	1850	1436	787	-373	4.0	1450	1650	8	-208	7.1	11.6	5.3	8.6	-2.3
6	141	29	68	+44	3.5	2320	1120	799	+401	4.5	1410	1210	16	+184	8.8	22.0	4.3	11.1	+6.5
7	141	51	80	+10	...	2320	1200	990	+130	...	1410	1450	18	-58	...	22.0	4.7	11.5	+5.8
8	141	69	66	+6	3.0	2320	1620	741	-41	3.6	1410	1745	9	-344	6.1	22.0	6.6	11.0	+4.4
9	141	66	72	+3	...	2320	1860	697	-237	...	1410	1550	10	-150	...	25.4	6.1	13.7	+5.7
10	141	51	69	+21	3.0	2320	1333	763	+224	4.3	1410	1425	8	-23	7.2	23.1	5.3	12.2	+5.7
11	141	43	82	+16	...	2320	1183	1048	+89	...	1410	1520	11	-121	...	22.0	5.0	12.6	+4.4
12	141	50	79	+12	3.0	2320	1260	998	+62	4.0	1410	1675	10	-275	8.1	22.0	5.3	12.6	+4.1
13	141	51	81	+9	3.2	2320	1510	966	-156	4.0	1410	1675	10	-276	8.0	22.0	5.7	13.4	+2.9
14	141	60	70	+11	...	2320	1625	759	-64	...	1410	1638	11	-239	...	22.0	5.8	12.2	+4.1
15	141	58	68	+15	3.3	2320	1480	801	+39	3.8	1410	1610	12	-212	7.3	22.0	5.5	12.4	+4.1
16	141	38	75	+27	3.7	2320	1325	848	+147	4.6	1410	1375	12	+23	8.2	22.0	4.7	12.7	+4.4

the serum potassium and phosphorus rose but slightly. When the administration of calcium salts was stopped, the serum calcium dropped. Starting on the 103rd day, 500,000 I. U. of vitamin D were given daily and the dosage was increased to 2,000,000 units daily on the 162nd day, to 4,000,000 units on the 170th day and the dosage decreased again to 2,000,000 units per day on the 182nd day. Following the institution of therapy with massive doses of vitamin D, the concentration of potassium, phosphorus and calcium in the serum rose progressively as shown in the chart. As has been previously mentioned, the patient showed marked

striped portion of the column represents the fecal excretion; the obliquely striped portion, the urinary excretion. The retention is thus indicated by the clear part of the column. A negative balance is shown by the dotted portion of the column extending above the intake line. Each column represents a single period. The spaces between columns represent periods during which the patient was maintained on a regimen identical with that of the following study period but during which no collections were made. Above each column is shown the concentration of the particular electrolyte in the blood serum as determined at the end of the period.

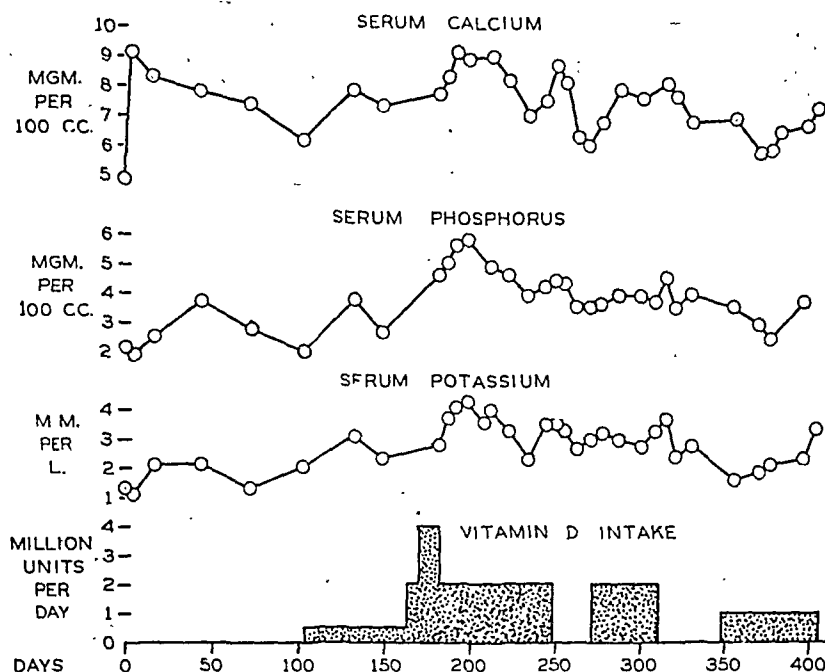


FIG. 1. The influence of vitamin D upon the concentrations of potassium, phosphorus and calcium in the serum.

The changes in the potassium, phosphorus and calcium balances with changes in diet and vitamin D are quite similar. During periods 1 and 2, there was considerable retention of potassium and phosphorus and the patient was essentially in equilibrium with respect to calcium. Following the substitution of starches for sugars in the diet, the diarrhea became more marked and during periods 3 and 4, the fecal loss of potassium, phosphorus and calcium increased. Associated with the increased loss of these substances from the body, the concentration of potassium in the serum decreased from 3.6 to 3.3 mM per liter, that of phosphorus from 5.2 to 4.7 mg. per 100 cc., and the serum calcium dropped from 9.1 to 8.3 mg. per 100 cc. When the fat intake was increased following period 4, the diarrhea became even more marked. The potassium excretion in the stools during period 5 was 50 mM per day, which was almost equal to the potassium intake of 60 mM. The urinary excretion of potassium decreased from an average of 87 mM per

day to 35 mM per day. There was still, however, a marked loss of potassium from the body and the serum potassium was reduced to 2.3 mM per liter by the end of period 5. There were also increased losses of phosphorus and calcium from the body during this period, with decreases in the concentrations of phosphorus and calcium in the serum to 4.0 and 7.1 mg. per 100 cc., respectively. During the eight days on this dietary regimen, the patient showed a recurrence of her muscular weakness. When the "optimal" diet was resumed at the end of period 5, there was again a rapid improvement in the patient's status, with a decrease in the diarrhea and increased muscular strength and sense of well-being. On this regimen during period 6, there was a considerable positive balance of potassium, phosphorus and calcium with a rapid increase in the concentration of these ions in the serum.

At the conclusion of period 6, the supplement of vitamin D, which the patient had been receiving for 144 days, was discon-

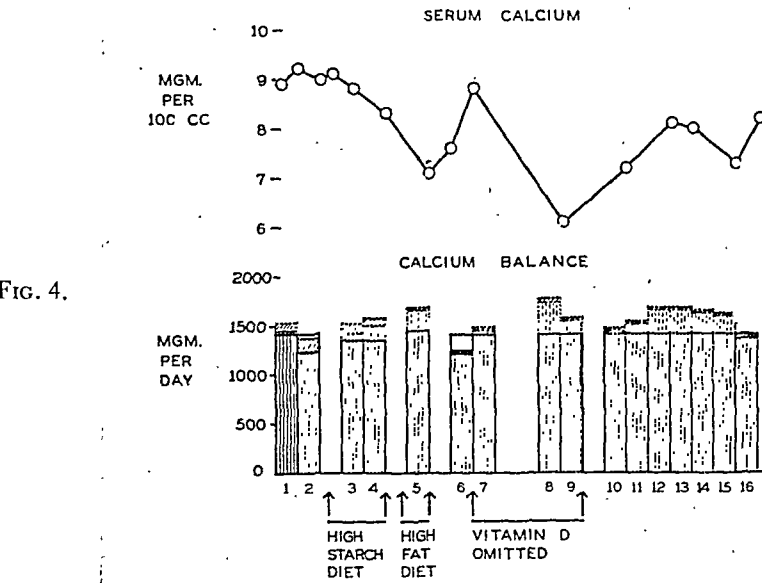
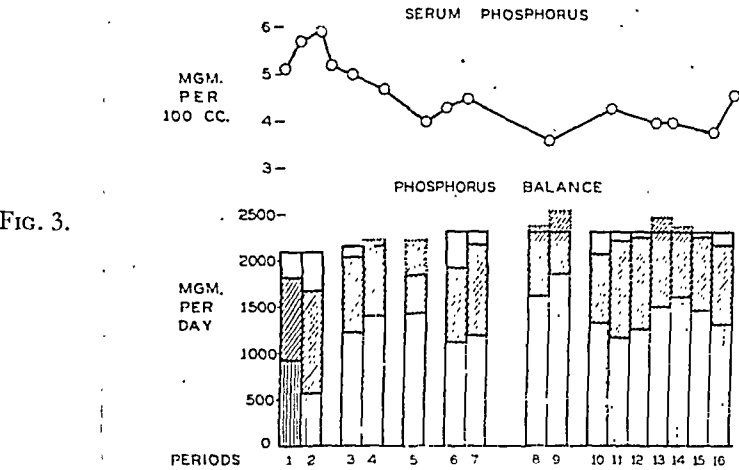
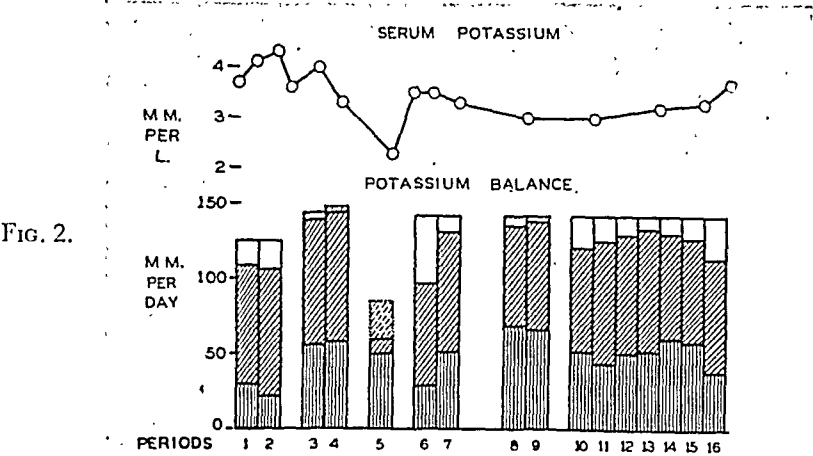


FIG. 2. The effect of variations in diet and vitamin D intake upon the potassium balance and the concentration of potassium in the serum. The vertically striped portions of the column represent the fecal excretion, the obliquely striped portion, the urinary excretion. The height of the column enclosed in solid lines indicates the daily intake, and the portions enclosed in dotted lines represent negative balances.

FIG. 3. The effect of variations in diet and vitamin D intake upon the phosphorus balance.

FIG. 4. The effect of variations in diet and vitamin D intake upon the calcium balance.

tinued. No other change was made in her regimen. An almost immediate exacerbation of the patient's diarrhea occurred, with a sharp increase in the fecal excretion of potassium as well as in the loss of phosphorus and calcium. At the end of period 9, vitamin D was again given daily in a dosage of 2,000,000 I.U. per day and definite improvement was noted. The fecal loss of potassium diminished and there was increased retention of potassium. A similar increase in the phosphorus balance occurred. The effect on the calcium balance was less evident. Nevertheless, the serum calcium rose from 6.1 mg. per 100 cc. at the end of period 8, to 8.0 mg. per 100 cc. by the end of period 13. It was evident, however, that the patient's improvement was not being maintained on this regimen as well as it had been at the onset of the metabolic studies. This suggested that the lesion responsible for the disturbance of intestinal function was progressing. Even at this stage, however, reduction of the fat intake to 50 Gm per day in period 16 resulted in increased retention of potassium, phosphorus and calcium associated with improvement in the diarrhea.

The influence of the diet and of vitamin D upon the diarrheal state are further shown by the fat, nitrogen and water content of the stools, which are indicated in Figure 5 as Gm. per day. Even during periods 1 and 2, when the patient was doing relatively well, the stool fat and nitrogen were above the normal values. Following increase of the starch intake in periods 3 and 4, there was a considerable rise in the loss of fat, nitrogen and water in the stools. The absolute loss of fat in the stools was further increased in period 5, when the fat intake was raised from 70 to 150 Gm. per day. Even more striking is the increased loss of water in the stools during this period. The improvement upon return to the low fat, low starch diet is reflected in the decrease

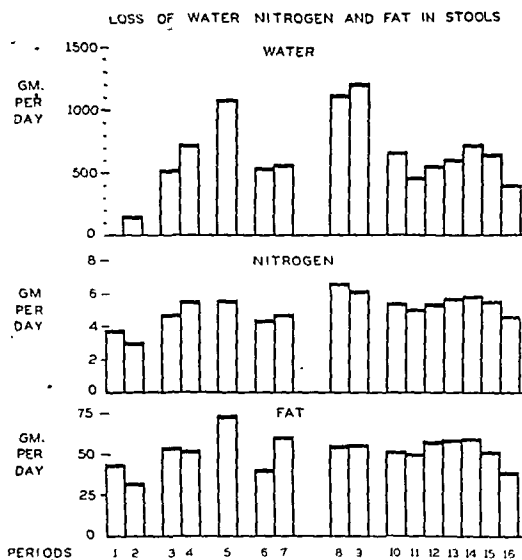


FIG. 5. The losses of fat, nitrogen and water in the stools as influenced by diet and vitamin D intake.

in stool fat, nitrogen and water during period 6. At the end of this period, the administration of vitamin D was discontinued and during periods 7, 8 and 9, the stool fat, nitrogen and water increased with subsequent improvement when vitamin D was resumed at the end of period 9. Despite the continued daily intake of 2,000,000 units of vitamin D daily, the losses of fat, nitrogen and water began to increase again but further improvement was obtained by reduction of the diet fat to 50 Gm. per day in period 16.

The concentrations of sodium and potassium in the stool water are shown graphically in Figure 6. The striped portions of the column represent the concentration of potassium and the clear segment of the column indicates the concentration of sodium. The sum of the concentrations of these two ions ranged from 130 to 177 mM per liter, with most of the values being in the neighborhood of 150 mM per liter. The concentration of the monobasic cations in the stool water is, therefore, approximately equal to the concentrations of monobasic cations in the extracellular water but the concentration of potassium



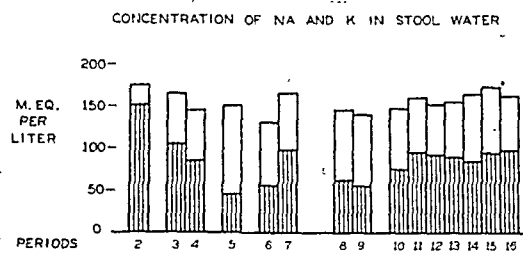


FIG. 6. The concentrations of potassium and sodium in stool water. The striped part of the column indicates the concentration of potassium and the clear portion the concentration of sodium, the total height of the column representing the sum of the concentration of these two ions.

is many times greater in the water of the stools than in the extracellular fluid of the body. The stool potassium was found to be in a diffusible state as indicated by ultrafiltrability through a cellophane membrane.

A deficit of extracellular potassium, as demonstrated by a reduction in the concentration of potassium in the serum, is seen to result from excessive loss of potassium in the stools. It can also be shown that in this patient a deficit of intracellular potassium is associated with decreased concentration of potassium in the extracellular fluid. In Table III the daily potassium and nitrogen balances are averaged for groups of experimental periods during which a given regimen was maintained. In column 1 are given the periods included in each group, in column 2 is shown the average potassium balance, and in column 3 is given the intracellular potassium balance. This is obtained by correcting the total potassium balance for the increase or decrease of extracellular potassium, which is calculated by multiplying the volume of extracellular fluid (0.2 body weight) by the change in concentration of the potassium in the serum during the periods included. No correction was made for change in volume of the extracellular fluid. By comparison with the total potassium balance, the changes in extracellular potassium are small. In column 4

is given the nitrogen balance and in column 5 the theoretical potassium balance calculated on the basis of 3 mM of potassium per Gm. of nitrogen retained or lost. This is approximately the proportion of potassium to nitrogen in intracellular fluid.<sup>9</sup> The “excess potassium” (column 6) is obtained by subtracting the theoretical potassium balance from the intracellular potassium balance. This value indicates the intra-

TABLE III  
INTRACELLULAR POTASSIUM EXCHANGE

Periods	Potassium Balance	Intra-cellular Potassium Balance	Nitrogen Balance	Predicted Potassium Balance	Excess Potassium
	mM Per Day		Gm./Day	mM Per Day	
1, 2	+18.6	+18.0	+4.8	+14.4	+ 3.6
3, 4	+ 3.6	+ 4.4	+2.3	+ 6.9	- 2.5
5	-25.4	-23.7	-2.3	- 6.9	-16.8
6	+43.8	+43.8	+6.5	+19.5	+24.3
7-9	+ 7.8	+ 8.2	+5.4	+16.2	- 8.0
10-15	+13.4	+13.4	+4.2	+12.6	+ 0.8
16	+26.6	+25.8	+4.6	+13.8	+12.0

cellular potassium not accounted for by destruction or repair of body tissue. During period 5, when the concentration of extracellular potassium decreased rapidly, intracellular potassium was lost in excess of the amount expected from the loss of tissue nitrogen. In period 6 the concentration of extracellular potassium was increased and intracellular potassium was retained in considerable amount. During periods 7, 8 and 9, the potassium retention was less than that expected from the nitrogen balance so that a loss of intracellular potassium occurred. When vitamin D was resumed in period 10, the potassium loss ceased and in period 16, there was a considerable increase in intracellular potassium. In general, in those periods in which the concentration of potassium in extracellular fluid dropped, potassium was also lost from the cells and an increase in concentration of extracellular potassium was associated

with retention of intracellular potassium. It cannot be determined from our data whether the loss or gain of intracellular potassium was associated with a change in amount of intracellular potassium or whether there was a change in concentration of potassium in the cells. Darrow<sup>9</sup> has reviewed the evidence indicating that potassium may be lost from the muscle cells with replacement by sodium under conditions of potassium deficit and that this process is reversed when potassium is restored.

At the conclusion of period 16 (312th day), the patient was maintained on the diet given during that period but the oral vitamin D was discontinued. Between the 323rd and 330th day, a total of 2,400,000 units of vitamin D was given by intramuscular injection. Despite this treatment, the serum potassium, phosphorus and calcium dropped progressively as shown in Figure 1. On the 348th day, oral vitamin D was renewed in a dosage of 1,000,000 units per day. After a period of about two weeks, the serum potassium, phosphorus and calcium began to increase again. These findings indicated that extremely large doses of vitamin D were necessary to maintain symptomatic improvement and that smaller amounts of vitamin D given parenterally were without effect.

In order to determine whether the vitamin D had been adequately absorbed, the vitamin D content of the blood serum was determined by bio-assay by the method of Warkany<sup>13</sup>. The serum from blood drawn on the 348th day contained approximately 1,000 units of vitamin D per 100 cc. This was at the end of the second period of vitamin D withdrawal and the patient had been given no extra vitamin D for 36 days except that given parenterally.

#### COMMENTS

In this patient with lymphosarcoma involving the wall of the small intestine and

the mesenteric lymph nodes, impairment of intestinal absorption of electrolytes was found to exist along with disturbances of absorption of fat and nitrogen. The defect of calcium and phosphorus absorption associated with fatty diarrhea is well known.<sup>5</sup> Potassium deficiency due to excessive loss of potassium in diarrheal stools has not been recognized as a possible occurrence in steatorrhea. It has long been known, however, that in acute diarrheal disease large quantities of potassium, as well as sodium, may be lost in the watery stools. The concentrations of potassium and sodium in the water of the stools of the patient reported here are similar to those found in acute diarrhea.<sup>10</sup> The disturbances of water and electrolyte absorption parallel to some extent the loss of unabsorbed fat and fatty acids in the feces. When the intake of starch was increased in periods 3 and 4, the loss of fat in the stools increased as did the loss of water, potassium, phosphorus and calcium. This deleterious effect of starch has been found in some cases of fatty diarrhea of unknown etiology classified under the names of celiac disease or idiopathic steatorrhea.<sup>4,25</sup> The increased fat intake and fecal fat during period 5 resulted in an even more marked loss of water in the stools and the loss of potassium in the stools was almost equal to the potassium intake.

The influence of vitamin D upon the intestinal absorption of water and electrolytes was quite striking in this patient. Bassett, Keutmann, Hyde and Van Alstine<sup>5</sup> studied the effect of the administration of 225,000 units of vitamin D daily to several patients with fatty diarrhea, hypocalcemia and hypophosphatemia. They found that vitamin D therapy not only resulted in increased concentrations of calcium and phosphorus in the serum but also in improvement in the diarrhea, with a reduction of the loss of water and nitrogen in the stools. This manifestation was considered by them to be

a non-specific effect of improvement in the patient's state.

In the present study, the bio-assay of the patient's serum thirty-six days after a period of intensive vitamin D therapy indicated that the vitamin D content of the serum was 1,000 units per 100 cc., about ten times the average value in normal adults not receiving extra vitamin D.<sup>32,33</sup> In arthritics given up to 500,000 units of vitamin D daily, concentrations of vitamin D in the serum as high as 9,000 to 13,000 units per 100 cc. have been found, with concentrations of 2,000 to 4,000 units one month after therapy was stopped.<sup>33</sup> It is likely that the vitamin D given to this patient was not completely absorbed. Lack of absorption alone, however, cannot explain the need for such large amounts of vitamin D. When the administration of vitamin D was discontinued the first time, the serum calcium and phosphorus dropped rapidly and the diarrhea became more marked within a few days. During the second period of lack of vitamin D, the serum calcium and phosphorus dropped despite the intramuscular injection of 2,400,000 units of vitamin D. The serum calcium was 6.9 mg. per 100 cc. at a time when the blood serum contained ten times the average normal concentration of vitamin D. The findings suggest that extremely high concentrations of vitamin D in the serum were necessary for the effect of vitamin D upon the intestinal function seen in this patient.

It is difficult to say to what extent the potassium deficiency shown by this patient contributed to her symptoms. Both she and a previous patient with potassium deficiency associated with the sprue syndrome<sup>17</sup> exhibited marked muscle weakness, hypoaactive deep reflexes and hypotension. In view of the other nutritional disturbances present due to the chronic diarrhea, one can only speculate about the possible relationship of potassium deficiency to the impairment of muscle strength. In dogs,

severe muscle weakness and paralysis may result from a diet low in potassium.<sup>27</sup> In man, the syndrome of familial periodic paralysis is known to be associated with reduction of the serum potassium.<sup>2,30</sup> Extremely low concentrations of serum potassium have been found, however, by Butler, Talbot and MacLachlan<sup>8</sup> in children given testosterone propionate without any symptoms which could be ascribed to the low concentrations of extracellular potassium. The decrease in extracellular potassium in patients receiving testosterone propionate was thought to be due to rapid synthesis of cell protein with retention of intracellular potassium. In the potassium deficiency resulting from loss of potassium in the diarrheal stools, the evidence indicates that loss of intracellular potassium is associated with deficiency of extracellular potassium. If potassium salts had been administered to these patients without other therapy, it might have been possible to ascertain whether any therapeutic effect was produced by replacement of the potassium deficit alone. Unfortunately, this was not done.

The disturbance of intestinal function in this patient was presumably the result of injury to intestinal mucosa by infiltration with lymphosarcoma and obstruction of the lymphatics. Obstruction of the pancreatic ducts was not present during the period of study as indicated by the normal content of pancreatic enzymes in aspirated duodenal contents.

#### SUMMARY

A patient with chronic diarrhea was studied who showed marked reduction of the concentrations of potassium, calcium and phosphorus in the serum, associated with excessive losses of fat, nitrogen, water, potassium, calcium and phosphorus in the stools. At autopsy, a lymphosarcoma of the small intestine and mesenteric lymph nodes

was found which was the basis for the disturbance of intestinal function.

Balance studies were made on various dietary regimens. These studies indicated that the loss of potassium in the stools was responsible for the reduction of serum potassium found in this patient. Comparison of the nitrogen and potassium balances indicated that during periods of potassium deficit, intracellular potassium was lost in excess of that expected from nitrogen loss.

The severity of the diarrhea was reduced by a diet low in fat and in starch. Large doses of vitamin D were found to be effective in further reducing the loss of water, potassium, calcium and phosphorus in the stools.

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# A Clinical Comparison of the Effectiveness of 6-n-Propylthiouracil and 2-Thiouracil as Antithyrototoxic Agents\*

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MANY compounds have now been tested for their goitrogenic influence upon small laboratory animals.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The activity of any particular substance seems to depend upon a —N—C—X group, where X is an N, O or S atom.

The most effective agents are those in which a complete thiourylene radical is present. Astwood found 115 of 220 compounds goitrogenically potent and twenty-five of these "as active or more active than thiouracil" weight for weight.<sup>1</sup> Of these twenty-five, 6-n-propylthiouracil (hereafter designated propacil) was the most powerful and eleven times as goitrogenic in the rat as 2-thiouracil (hereafter designated thiouracil).<sup>1</sup>

Inasmuch as results in the animal cannot be depended upon to hold for the human being, extensive clinical trial and comparison must be carried out for each individual agent which appears promising for its antithyrototoxic effect. For instance, Astwood's report<sup>9</sup> indicates that propacil does not compare as favorably with thiouracil in man as it does in the rat, being only five times as active as the latter in the control of toxic goiters. In view of the all too frequently occurring severe reactions<sup>10, 11, 12, 13</sup> to thio-

uracil, any less toxic agent such as propacil has been shown to be in preliminary clinical trial<sup>9, 14, 15</sup> will be especially welcome for the management of thyrotoxic subjects. The present analysis of cases in which the patients were treated with propacil may encourage its more widespread application in the management of hyperthyroidism.

## MATERIALS AND METHODS

Eighteen male and fifty-seven female subjects with thyrotoxicosis were studied while

TABLE I  
AGE AND SEX DISTRIBUTION IN SEVENTY-FIVE CASES OF  
THYROTOXICOSIS TREATED WITH 6-N-PROPYLTHIOURACIL

Type of Goiter	Total No.	Male		Female	
		Age (Yr.)		Age (Yr.)	
		No.	Range Av.	No.	Range Av.
Hyperplastic..	41	8	27-52 41.3	33	18-47 39.8
Nodular.....	34	10	29-51 53.4	24	23-75 48.2

under treatment with propacil (Table I) for periods ranging from two to twelve months. Thirty-three of these were hospitalized for varying periods in order to allow more thorough investigation but without relation

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necessarily to the degree of toxicity exhibited by them. Propacil was administered in 25 mg. tablets\* from one to several times daily.

The criteria necessary to establish a diagnosis of toxic goiter and other features of the regimen, including a description of the laboratory methods used, have been previously described.<sup>11,16</sup>

### RESULTS

In all, propylthiouracil has been administered to more than 100 patients. However, guided by the experience of others,<sup>9</sup> we used too little of the drug at first so that some of these patients were operated upon or returned to the use of thiouracil.

### CLINICAL DATA

In the seventy-five patients whose symptoms of toxic goiter were brought fully under control by the drug, the symptoms and qualitative therapeutic responses were similar in every regard to those obtained with thiouracil. These were detailed at some length for the latter drug in a previous study.<sup>11</sup> Therefore, only the more essential data will be included here.

The women ranged in age from eighteen to seventy-five years, the men from twenty-seven to fifty-two (Table I), with averages of 40.7 and 46.9 years, respectively. Fifty-one had a predominantly hyperplastic gland; thirty-four had a nodular type of goiter. The response of the basal metabolic rate in relation to dosage is shown graphically in Figure 1 and closely follows the "iodine decay curve" of Means and Lerman.<sup>17</sup> The average initial or pretreatment basal metabolic rate in forty-two previously uncontrolled patients was plus 49.0 per cent; when fully controlled, the average rate was plus 8.6 per cent.

\* Generous supplies of 6-n-propylthiouracil were courteously supplied by Dr. Stanton Hardy of the Lederle Laboratories. Recently this material has been available as a 50 mg. scored tablet, so that doses of 25 mg. may be easily administered.

### DOSAGE

In regard to dosage, our patients may be divided into two groups: (1) forty-two who had received no previous chemotherapy and (2) thirty-three who had been previously rendered non-toxic by the administration of thiouracil.

In the first group, effective initial daily doses ranged from 75 to 250 mg. with an average of 165 mg. (Fig. 1.) For both groups the maintenance dose varied from 25 to 75 mg., with an average of 55 mg. per day.

The time necessary to bring about complete control in the patients who had not previously received thiouracil varied from two to seven weeks, being generally, although not invariably, longer with the smaller initial doses. However, each of the ten patients who received 200 mg. or more daily at the beginning was controlled in four weeks or less.

The doses necessary to maintain a normal production of thyroid hormone in the thirty-three patients previously controlled by thiouracil varied from 25 to 100 mg. daily. The actual amount given was perhaps less informative than the ratio of that amount to the dose of thiouracil previously required. That ratio varied from 1:1 to 1:4. (Table II.) In general it would appear that ratios of from 1:2 to 1:3 were most effective. In other words, weight for weight, propacil is from two to three times as effective as thiouracil.

TABLE II  
WEIGHT RATIO OF EFFECTIVE DOSES OF 6-N-PROPYLTHIOURACIL AND 2-THIOURACIL IN THIRTY-THREE PATIENTS

Propacil:Thiouracil Ratio . . .	1:1	3:4	1:2	1:2.5	1:3	1:4
No. Cases . . . . .	1	1	12	6	8	5

From our experience with more than 100 patients treated with propacil and over 200 treated with thiouracil, we have found the

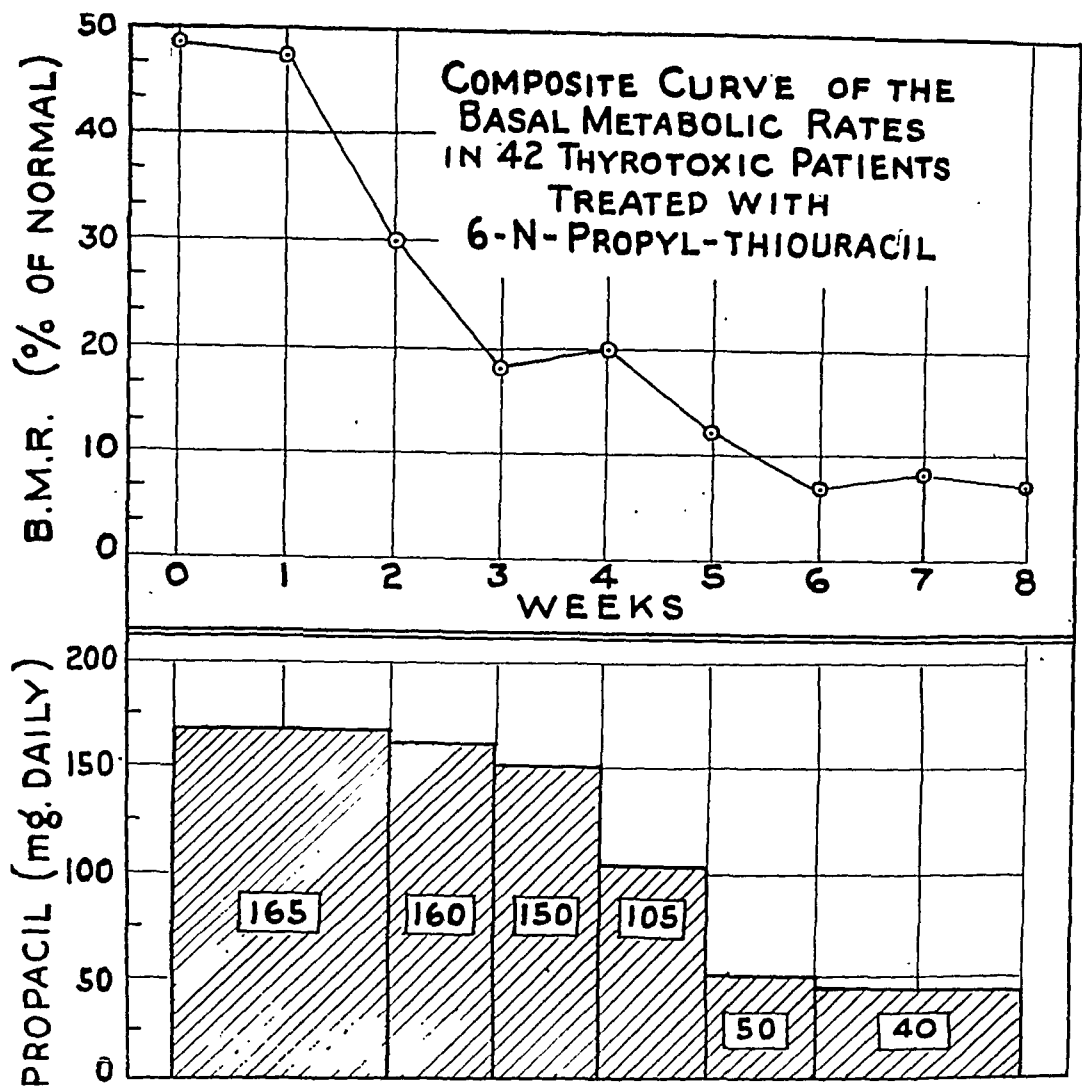


FIG. 1.

regimen of dosage indicated in Table III satisfactory. The largest doses mentioned,

TABLE III  
SUGGESTED REGIMEN FOR EFFECTIVE ADMINISTRATION OF  
6-N-PROPYLTHIOURACIL, COMPARED WITH 2-THIOURACIL

Period of Treat- ment (Days)	Thiouracil (Gm.)	Propacil (Gm.)
0-7	0.8*	0.250*
0-14	0.6	0.200
14-Control (14-49)	0.4	0.200
Maintenance	0.1-0.3	0.025-0.075

\* These dosages may never be necessary. We have employed them when rapid "saturation" with the drug seem particularly important.

800 and 250 mg. daily for thiouracil and propacil respectively are always employed

for a predetermined limited time only, which in any event should not exceed seven days. The method of slowly reducing the maintenance dose until the drug is omitted entirely is described below under Remissions (q.v.).

TOXICITY

In seventy-five patients, we have encountered but one reaction to propacil. This appeared in a forty-eight-year old woman with a so-called "postmenopausal type" of toxic nodular goiter. When first observed, she showed the majority of the toxic symptoms and signs originally described by Plummer. Various laboratory analyses were confirmatory, including a basal metabolic

rate of plus 43. Therapy with thiouracil had been attempted previously. On the fifth day of treatment with 0.6 Gm. daily of that drug she developed slight fever, and on the seventh day an accompanying generalized urticaria with the temperature up to 104.2°F. Five weeks later, she was given 50 mg. of propacil daily. On the seventh day after this was begun, she complained of generalized itching. By the ninth day, there was a return of the generalized rash and fever, the whole picture closely resembling that seen when she was treated with thiouracil, although less marked in degree.

#### REMISSIONS

Much has been written about the tendency for the symptoms of hyperthyroidism to recur following cessation of treatment with thiouracil or one of its closely related derivatives. We believe this can be avoided in a large percentage of cases if attention is paid to certain details of treatment. After the patient has received a maintenance dose of propacil (Table III) for three months or more, it is our practice to decrease the dose by 25 mg. daily. At each succeeding monthly visit a similar reduction is made, until the patient has been maintained for one month on a single tablet of 25 mg. daily. Then, for an additional month, 25 mg. is administered every other day. If at the end of that time no symptoms or signs of thyrotoxicosis are apparent and the basal metabolic rate is normal, the drug is stopped. If at any time during the "reduction treatment" symptoms or signs of toxicity recur, the dosage is "stepped up" to the immediately preceding level and kept there until the clinical condition has remained satisfactory for three months. However, should signs of hypothyroidism occur earlier than this, the dose is accordingly reduced to restore the thyroid status to normal.

By following this regimen, we have been able to discontinue propylthiouracil in ten

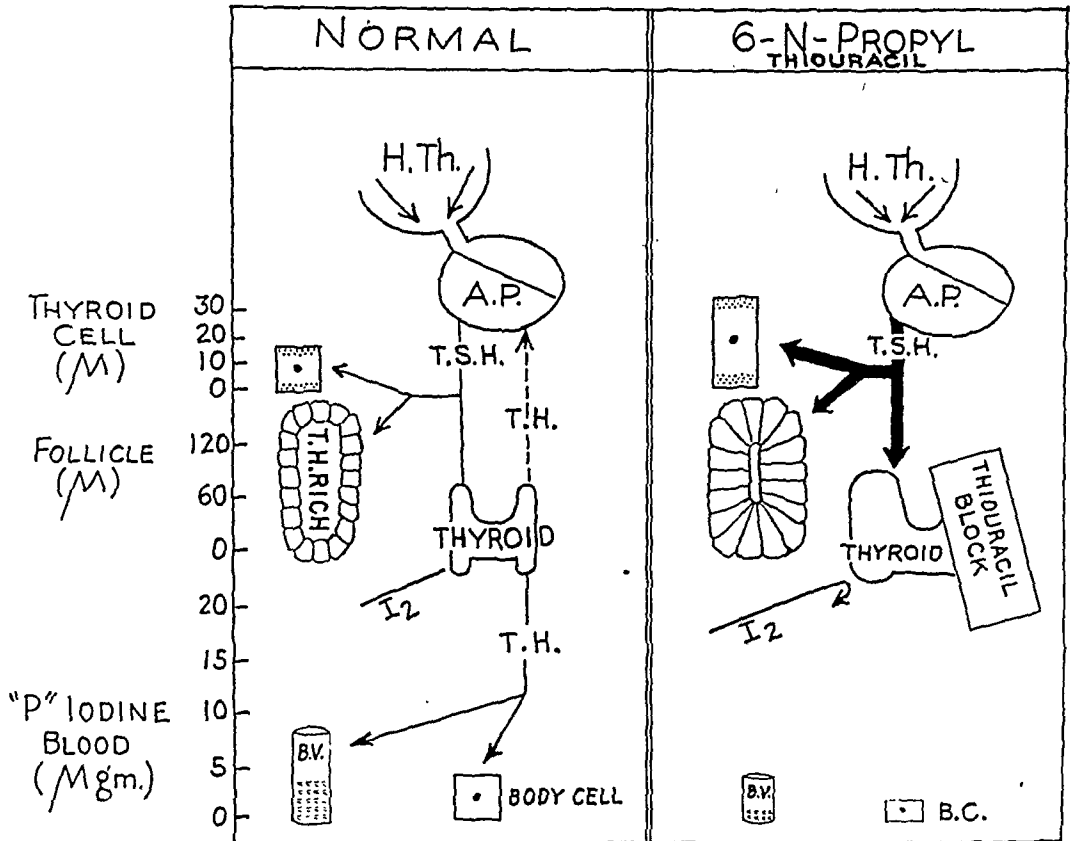
of the seventy-five patients without recurrence. However, since the drug has been available to us for slightly less than one year, we have been able to follow these "recovered" cases only for approximately four months following cessation of treatment. Inasmuch as all our patients were not started on the drug simultaneously at the beginning of the year, the above figure actually represents approximately 60 per cent of the group which has completed the regimen of dosage outlined above.

#### COMMENTS

The influence of thiouracil and its derivatives upon the pituitary-thyroid system has been explained by Means<sup>18</sup> according to the schematic representations of Galli-Mainini.<sup>19</sup> In accordance with this concept, the normal relationships between the hypothalamus, the pituitary, the thyroid and the fluids and tissues of the body may be diagrammatically indicated as in Figure 2. The alterations produced by propacil are shown for comparison in Figure 2. It will be seen that the action resembles that of thiouracil in every respect. The uptake of iodine by the thyroid gland is decreased. The formation of thyroid hormone is prevented. Therefore, the unopposed anterior pituitary secretes a greater amount of thyroid-stimulating hormone than normally. The thyroid cell changes to a high columnar type. The thyroid follicle enlarges. Its colloid is extruded and little if any is formed to take its place. In the face of this thyroid hyperplasia, there is a lack of thyroid hormone, with a consequent decrease in the protein-bound iodine of the blood and a decreased activity of the tissue cells. It must be emphasized that propacil appears not to effect a fundamental cure in thyrotoxicosis, any more than other commonly employed methods. Nevertheless, it "throws a block across the thyroid," preventing the manu-



PITUITARY-THYROID-TISSUE RELATIONSHIPS  
UNDER NORMAL CONDITIONS AND FOLLOWING  
THE ADMINISTRATION OF PROPYL-THIOURACIL



H.Th.=HYPOTHALAMUS; A.P.=ANTERIOR PITUITARY; T.S.H.=THYROID STIMULATING HORMONE OF THE PITUITARY; T.H.=THYROID HORMONE;  $I_2$ =IODINE; B.V.=BLOOD VESSEL; B.C.=BODY CELL.

FIG. 2.

facture of thyroglobulin. Thus it breaks the vicious cycle of disturbed hypothalamic-pituitary-thyroid relationships which cause the toxic state. When the patient is no longer toxic, proper care can be given to the underlying mental and emotional problems without fear of further damage.

Within the limits just implied, the present studies and the clinical trials of other workers<sup>9,14,15</sup> indicate that propacil (6-n-propylthiouracil) will prove clinically useful in the management of all forms of thyrotoxicosis. It appears to be far superior to thiouracil. In animals the lethal dose (L.D.-50) is slightly less than that of thiouracil and its goitrogenic activity approximately eleven times that of thiouracil. In earlier studies in the human being, propacil was thought to

be approximately five times as effective as thiouracil<sup>9</sup> but such an estimate requires downward revision in the light of the present and other data;<sup>14,15</sup> it appears to be from two to three times as effective as thiouracil, weight for weight.

Moreover, in any range of effective dosage, propacil appears to be far less toxic than thiouracil. Astwood and VanderLaan<sup>14</sup> report no ill effects in their first 100 patients. McCullagh and his associates<sup>15</sup> discontinued the drug in one of 110 patients treated because "mild sore throat and a fall in leukocyte count followed repeated trials." Both the groups of workers just mentioned have used propacil successfully in patients that developed severe reactions to other thiouracil-related compounds.

One patient in the present series, already shown to be sensitive to thiouracil, also developed a reaction to propacil. Untoward effects were not encountered in any other patient. Such low toxicity contrasts sharply with thiouracil, under treatment with which from 12 per cent to 13.1 per cent of all patients developed some untoward manifestation<sup>10,11,13</sup> and 2.5 per cent exhibited the more serious febrile or granulocytopenic reactions. Death from granulocytopenia has been reported in about 0.5 per cent of patients treated with thiouracil.<sup>10</sup> Neither complete agranulocytosis nor death has yet been reported due to propacil. Since such a reaction is probably due to true toxicity rather than to drug hypersensitivity, it should occur rarely if at all in any range of dosage of propacil necessary to achieve an optimum therapeutic effect.

In conclusion, we believe that propacil is a relatively safe drug for the management of thyrotoxicosis of all types. It should replace operative interference except in those instances in which local pressure symptoms occur or unsightliness of the neck makes elective surgery highly desirable.

#### SUMMARY

1. Seventy-five patients with thyrotoxicosis have been successfully controlled by the use of 6-n-propylthiouracil (propacil) in initial doses varying from 75 to 250 mg. and maintenance doses of from 25 to 75 mg.

2. One severe febrile reaction was encountered in a patient who had previously developed a similar response to thiouracil.

3. Ten of the seventy-five patients have had no recurrence of thyrotoxic symptoms four months after discontinuing the drug.

4. It is concluded that 6-n-propylthiouracil is a safe and effective drug for the management of all forms of hyperthyroidism.

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# Thiouracil: Remission or Relapse of Hyperthyroidism after Discontinuing Its Use\*

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THIOURACIL has been used in the treatment of hyperthyroidism for a sufficient length of time so that its place in the therapy of this disease should now be evaluated. All investigators agree that hyperthyroidism, irrespective of type or severity, can, by an adequate daily dose of thiouracil, be brought under complete control. Thiouracil has proved to be of great value in preparing patients<sup>1,2</sup> with severe hyperthyroidism for thyroidectomy since multiple-stage operations, postoperative reactions with morbidity and mortality can be completely prevented in these patients who are properly treated. Thiouracil has been used for long-continued maintenance treatment of hyperthyroidism but this type of therapy entails close observation because of the possibility of toxic reaction. As regressive changes are not produced in the hyperplastic thyroid gland following thiouracil administration, permanent cure of hyperthyroidism is not to be expected. The clinical course after withdrawal of treatment of patients whose disease has been controlled by thiouracil is the subject of this report.

Astwood<sup>3</sup> has reported that after controlling hyperthyroidism for a prolonged period, from six to nine months, thiouracil could then be discontinued and in a high percentage of patients a remission would be

sustained. He emphasized prolonged treatment as the prerequisite for obtaining a prolonged remission. Reports by other observers<sup>3-13</sup> (Table 1) vary widely regard-

TABLE I  
REMISSIONS AND RELAPSES AFTER WITHDRAWAL OF THIOURACIL

Authors	No. of Cases	Remission		Relapse	
		No.	Per Cent	No.	Per Cent
Astwood.....	18	9	50	9	50
Rose and McConnell....	21	8	38	13	62
Gabrilove-Kert-Soffer...	5	4	80	1	20
Reveno.....	5	1	20	4	80
Palmer.....	10	5	50	5	50
McGavack-Gerl-Morton-Vogel-Schwimmer	"ability to discontinue the drug in the average case without recurrence of symptoms has varied widely"				
				2	
Watson.....	6	5	83	1	17
Barr, Shorr.....	47	36	77	11	23
Fishberg, Vorzimer.....	41	16	39	25	61
Williams et al.....	100	49	49	51	51
Total cases.....	253	133	54	120	46

ing remissions and relapses after withdrawal of treatment. Prolonged remissions were reported by various authors to occur in from 20 to 82 per cent and relapses in from 18 to 80 per cent of the patients treated. Although little significance can be given to the wide variation found in the smaller series of cases

\* From the Lahey Clinic. Read before the Section on Experimental Medicine and Therapeutics, American Medical Association, San Francisco, July 3, 1946.

reported, cases in the larger series were found to vary just as widely. Those authors reporting forty or more hyperthyroid patients found remissions in from 39 to 70 per cent and relapses in from 23 to 61 per cent. Most authors reported no relationship between the duration of treatment and the development of remission or relapse. McGavack<sup>8</sup> and his coworkers stated that the "ability to discontinue the drug in the average patient without recurrence of symptoms varied widely." Barr and Shorr<sup>10</sup> noted that the severest cases and particularly those patients who had recurrences after previous thyroidectomy had relapse almost as soon as treatment was stopped. Reveno's<sup>6</sup> studies led him to conclude that a prediction could not be made as to when and in which cases the drug may be stopped without relapses. He recommended thiouracil only for maintenance treatment.

The most complete work on this subject is that by Williams<sup>12</sup> who studied 100 hyperthyroid patients who had received prolonged thiouracil treatment. Of these, forty-nine have gone three to twenty-one months without treatment and have not had relapse. Fifty-one patients had relapse of hyperthyroidism after two weeks to five months. Of these, 66 per cent had relapse in one month. Williams<sup>12</sup> noted that the age of the patient, duration or type of hyperthyroidism did not influence relapse. Male patients had relapse of hyperthyroidism more often than female patients. The longer treatment was carried out, the lower the initial basal metabolic rate and the smaller the thyroid gland, the greater was the chance of remission. Patients with thyroid glands three to four times normal size did have sustained remissions, however, as did patients with initially high basal metabolic rates. There was no relation of relapse or remission to the dosage of thiouracil given or the speed of improvement. Of the total 253 cases reported by nine authors, 53.9 per cent re-

mained in remission and 46 per cent had relapse.

Experience with twenty-one patients who have been observed for as long as two and a half years from the standpoint of remission or relapse after withdrawal of thiouracil is the basis of this report. All of the patients had primary hyperthyroidism; eleven had recurrent hyperthyroidism. Treatment with thiouracil was begun in all patients in the dose of 0.6 Gm. a day and in some patients it was continued at this dose up to the time of its withdrawal. In other patients the dose of thiouracil was gradually decreased as improvement was noted. Thiouracil was administered for as long as twenty months in one case; the shortest treatment was two months. After withdrawal of treatment, eight patients remained in remission and thirteen patients suffered relapse of hyperthyroidism.

TABLE II  
REMISSION AFTER WITHDRAWAL OF THIOURACIL

Case	Age and Sex	Duration of Hyperthyroidism	Duration of Treatment	Duration of Remission	Initial BMR	Last BMR	Thyroid Enlargement
1	23 F	3 mo.	10 mo.	14 mo.	+27	-1	Slight
2	58 F	1 yr.	6 wk.	19 mo.	+25	+7	Slight
3	73 F	7 mo.	11 mo.	13 mo.	+19	+8	Small remnant
4	20 F	1 yr.	5 mo.	17 mo.	+28	+8	Slight
5	30 F	6 mo.	14 mo.	3 mo.	+35	+5	Slight
6	60 F	6 mo.	1 mo.	23 mo.	+17	-1	Slight
7	12 F	3 yr.	21 mo.	3 mo.	+23	+2	Small remnant
8	18 F	3 mo.	7 mo.	14 mo.	+27	+4	Small remnant

The eight patients (Fig. 1, Table II) who have remained in remission include five with initial primary hyperthyroidism and three with recurrent primary hyperthyroidism. All were females with a wide range of ages, twelve to seventy-three years. These patients had hyperthyroidism from three months to three years; five had the disease for seven months or less, the average dura-

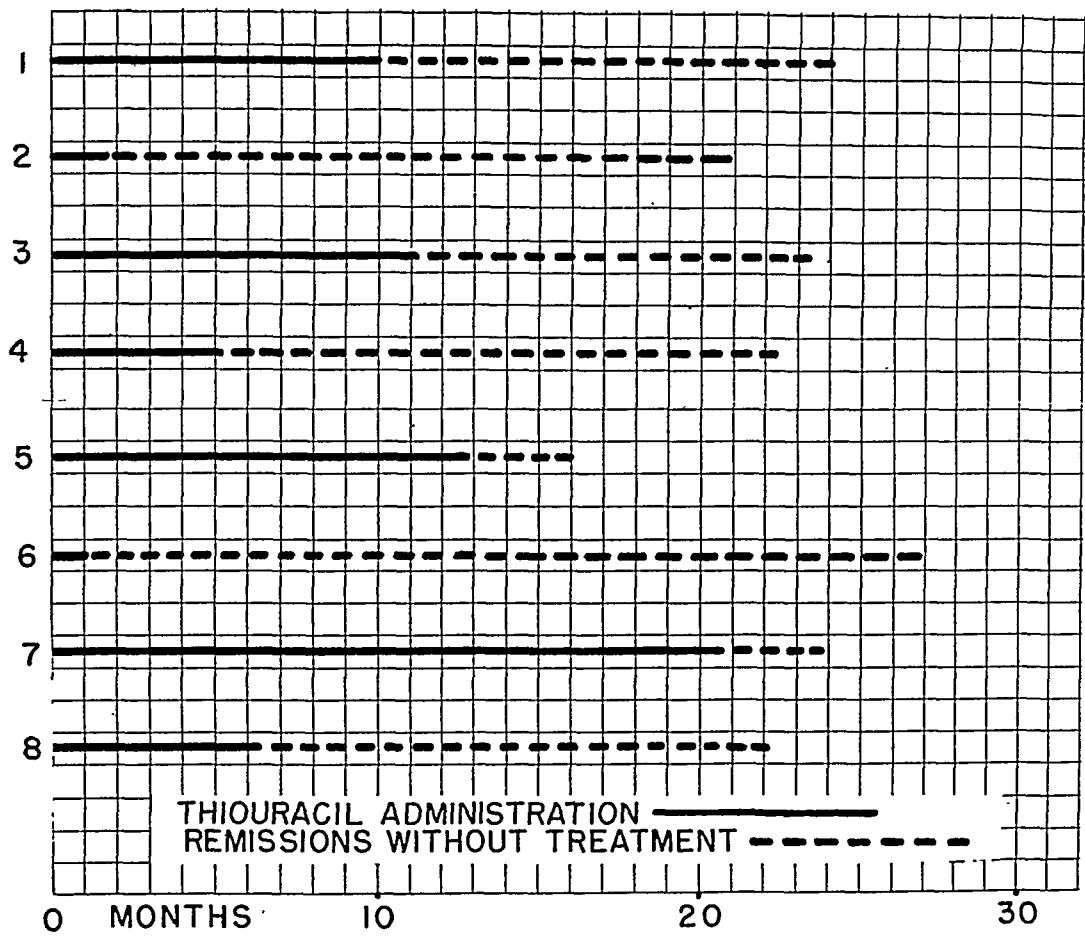


FIG. 1. Duration of thiouracil therapy in eight hyperthyroid patients and length of remission after withdrawal of treatment.

tion being eleven months. Thiouracil was administered for one to twenty-one months, the average time being nine months. The basal metabolic rate before treatment ranged from +17 to +35, the average being +25. The thyroid gland of all these patients was only slightly enlarged or the remnants were small. Remissions of nine months' duration or more occurred in six patients and of three months' duration in two patients. These latter two patients may still have a relapse. The average duration of remission is thirteen months.

The thirteen patients (Fig. 2, Table III) having relapse after withdrawal of thiouracil include nine patients with recurrent primary hyperthyroidism and four patients with initial primary hyperthyroidism. The age of these patients varied from twenty-seven to fifty-five years, the average being

forty years. Nine were female patients and four were males. Hyperthyroidism had been present for one month to five years, an average of fourteen months. Eight patients had hyperthyroidism for six months or less. Treatment was given for a period of two and a half to eighteen months, the average being eight months. The average basal metabolic rate was +30; 7 had a basal rate over +30. The thyroid glands or remnants were medium to large in size in twelve of the patients in this group; one patient (Case 13) had only slight enlargement of the thyroid. Relapse occurred in all from one to twelve months after withdrawal of thiouracil, the average being three and one half months; eleven had a relapse in one to six months. In two of the patients treated for fourteen to eighteen months, relapse occurred after two months. Of the thirteen patients having

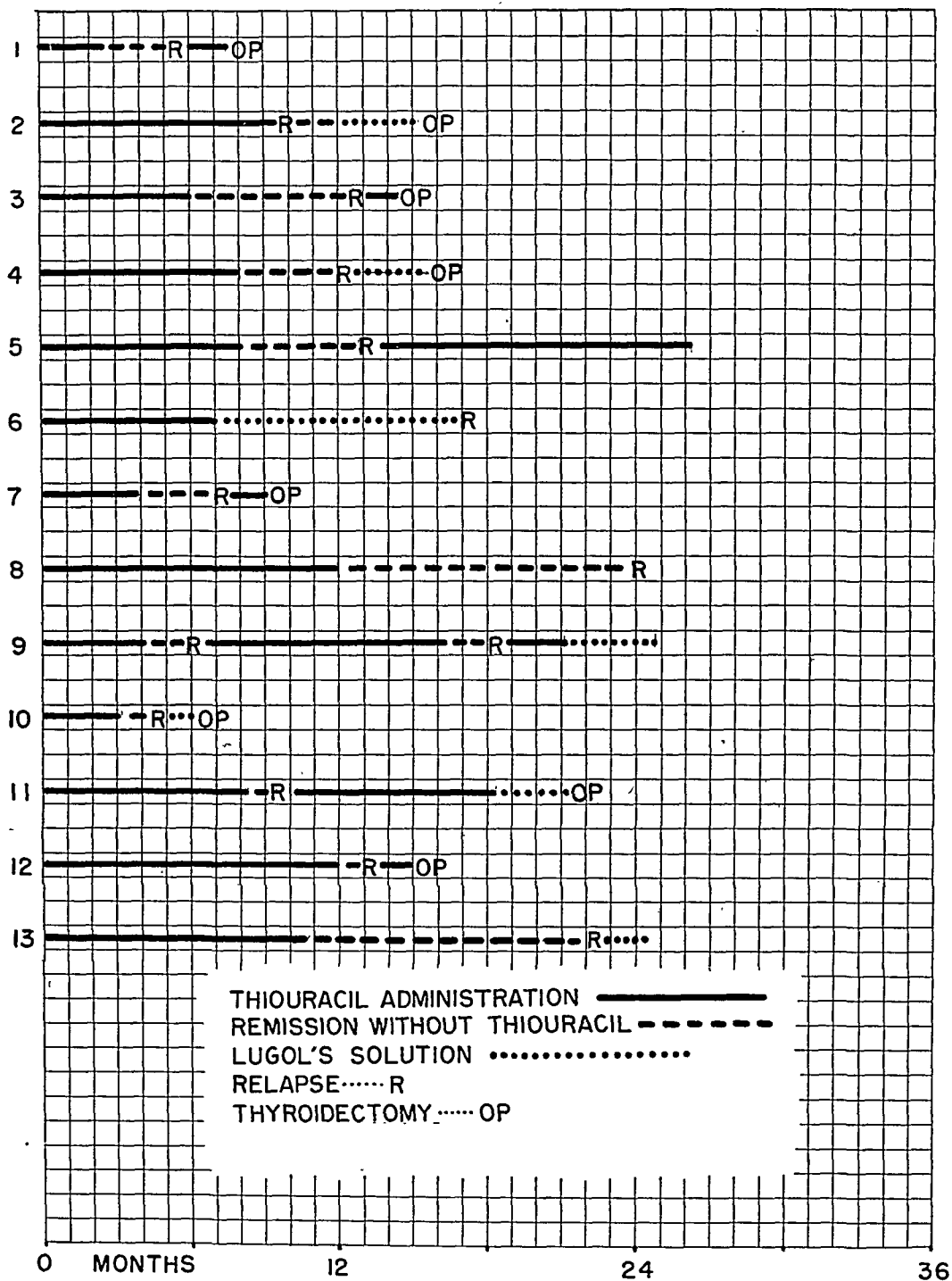


FIG. 2. Duration of thiouracil therapy in thirteen hyperthyroid patients, with remission and then relapse after withdrawal of treatment.

relapse, eight have had thyroidectomy; one is being maintained on thiouracil and three are receiving Lugol's solution.

A comparison of the two groups of patients (Table IV), those having sustained remission and those having relapse, reveals

that the patients who had relapses were slightly older and had hyperthyroidism of slightly longer duration; the difference, however, was not significant. The duration of treatment with thiouracil was approximately the same in the two groups. Male

TABLE III  
RELAPSE AFTER WITHDRAWAL OF THIOURACIL

Case	Age and Sex	Duration of Hyperthyroidism	Duration of Treatment	Onset of Relapse	Initial BMR	Thyroid Enlargement	Thyroid Tissue Removed at Thyroidectomy	
							Weight	Size, cm.
1	49 M	6 mo.	2 mo.	2 mo.	+45	Moderate	40 Gm.	7 × 3.5 × 2 6 × 3 × 1.5
2	55 M	4 yr.	10 mo.	2 mo.	+46	Moderate	50 Gm.	6 × 3 × 2 6 × 3 × 2
3	47 F	6 mo.	6 mo.	6 mo.	+45	Medium remnant	10 Gm.	3 × 2 × 1 2 × 2 × 1
4	33 F	3 mo.	8 mo.	4 mo.	+38	Medium remnant	15 Gm.	7 × 2 × 2
5	48 F	2 mo.	8 mo.	4 mo.	+26	Medium remnant		
6	42 F	6 mo.	7 mo.	1 mo.	+18	Medium remnant		
7	31 M	2 yr.	18 mo.	2 mo.	+41	Large	115 Gm.	9 × 5 × 3 10 × 5 × 2.5
8	31 F	1 yr.	12 mo.	12 mo.	+30	Medium remnant		
9	54 F	2 mo.	4 mo.	2 mo.	+3	Medium remnant		
10	42 F	13 mo.	3 mo.	1 mo.	+14	Medium remnant	10 Gm.	
11	27 F	1 mo.	8 mo.	1 mo.	+17	Medium remnant	12 Gm.	4 × 2 × 2 3 × 2 × 1.5
12	37 M	5 yr.	14 mo.	1 mo.	+35	Large remnant	55 Gm.	8 × 5 × 3 4 × 3 × 2 4 × 3 × 2
13	27 F	3 mo.	10½ mo.	11 mo.	+13	Small		

TABLE IV  
COMPARISON OF RELAPSE AND REMISSION GROUPS

	No. of Cases	Av. Age, Yr.	Sex	Duration of Hyperthyroidism	Duration of Treatment	Initial BMR	Thyroid Enlargement	Duration of Remission
Group obtaining remission.	8	36	F	3 mo. to 3 yr.	1 mo. to 21 mo.	+17 to +35	Slight	Av. 13 mo.
				Av. 11 mo.	Av. 9 mo.	Av. +25	Small remnants	
Group suffering relapse.	13	40	9F 4M	1 mo. to 5 yr.	2 mo. to 18 mo.	+3 to +46	Medium to large	1 mo. to 12 mo.
				Av. 14 mo.	Av. 8 mo.	Av. +30	Large remnants	Av. 3½ mo.

patients tended to have relapse of hyperthyroidism more than did female patients. Seventy per cent of the patients having relapse had recurrent hyperthyroidism, as against 37 per cent in the group remaining in remission. Most of the relapsing group had higher basal metabolic rates and moderate to large thyroid glands or remnants. Eight of the patients having relapse had subtotal thyroidectomy or removal of thyroid remnants. The amount of the thyroid tissue removed at operation varied in weight from 40 to 115 Gm., the remnants from 10 to 12 Gm., which represents a substantial amount of thyroid tissue since the normal thyroid gland weighs from 16 to 24 Gm.

#### SUMMARY

Patients with primary hyperthyroidism may have a prolonged remission from hyperthyroidism after withdrawal of thiouracil. Of the twenty-one patients observed, eight (32 per cent) remained in remission and thirteen (62 per cent) had a relapse. The duration of thiouracil administration after restoration of the basal metabolic rate to normal was not a factor in determining the duration of remission since prolonged remissions occurred after short therapy and prompt relapse was observed after long treatment.

Clinical experience indicates that patients with mild primary hyperthyroidism may occasionally have a prolonged remission either spontaneously or following brief iodine therapy, and that such a remission may last many years. Therefore, thiouracil in a sense might be classified with iodine in its power to cause a remission in mild hyperthyroidism and if the eight patients now in remission are observed sufficiently long, all can be expected to have a relapse.

Relapse of hyperthyroidism after withdrawal of thiouracil can be expected to occur in one to two months and not later than six months after withdrawal of treatment in patients having large thyroid glands or large recurrent remnants, in whom the basal metabolic rate is in the higher range. The basic etiologic factor which causes hyperthyroidism, which at present cannot be assayed, is, of course, the determining cause of recurrence or remission, and this factor is not affected by thiouracil therapy.

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Brucellosis and Infection Caused by Three Species of Brucella\*

Clinical, Laboratory and Epidemiological Observations

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BRUCELLOSIS of man or undulant (Malta) fever is with few exceptions a disease of sporadic occurrence. Ordinarily, very few cases are reported from an average rural county during the course of an entire year. Exceptions to this rule are (1) the greatly increased morbidity among persons whose occupation brings them into close contact with animals at the time of slaughter and (2) the certainty of multiple cases when the more virulent porcine species of brucella contaminates a raw milk supply. Illness from this disease is always traceable to infection in animals and is not known to be communicable from person to person. Direct contact with infected animals and the use of raw dairy products from infected dairy cows provide the main avenues of transmission to man. The attack rate is highest among individuals (such as packing house employees, male farm workers, veterinarians), whose occupation brings them into direct contact with infected animals, and lowest among urban residents who use none but pasteurized dairy products and who give no history of handling livestock.

During the fourteen-year period 1930 to 1943, reported cases of brucellosis of man in the United States totalled 36,513, an average annual morbidity rate of but two per

100,000 population. As might be expected, the disease shows relatively higher incidence in hog,† cattle and sheep raising areas, notably the West North Central and West South Central States. (Table I.)

TABLE I  
BRUCELLOSIS IN THE UNITED STATES, 1930-1943  
Morbidity for the fourteen-year period as reported from various sections of the country, and average annual rates per 100,000 population

Area	Population (1940 Census)	1930- 1943 Total Cases Reported	Average Annual Cases	Annual Rate Per 100,000
New England.....	8,437,290	2,458	175.5	2.08
Middle Atlantic.....	27,539,487	4,971	355.1	1.29
East North Central.....	26,626,342	6,828	487.7	1.83
West North Central.....	13,516,990	7,107	507.6	3.76
South Atlantic.....	17,160,060	2,929	209.1	1.22
East South Central.....	10,778,225	1,479	105.6	0.98
West South Central.....	13,064,525	6,105	436.1	3.34
Mountain.....	4,150,003	1,157	82.6	1.99
Pacific.....	9,733,262	3,479	248.4	2.56
U. S. A. Total.....	131,006,184	36,513	2608.0	1.99

Data presented in Table I were compiled from totals of reported cases in each state, supplied through courtesy of state health officers of the forty-eight states.

Considering individual states, the lowest rate for the twelve-year period 1930 to

† The swine population in Iowa was approximately 20,000,000 in the peak years 1943 and 1944, estimated as 20 per cent higher than during pre-war years. (From data furnished through courtesy of C. C. Franks, D. V. M., State Veterinarian, Iowa State Department of Agriculture.)

\* From the Division of Preventable Diseases, Iowa State Dept. of Health and the Iowa State Hygienic Laboratory.

1941, namely 0.4 per 100,000, was in North Carolina, significantly the only state at the time to be accredited in measures for the eradication of brucellosis in dairy cattle. Considering the reported occurrence of cases, hogs are apparently a minor source of infection in that state.

The annual morbidity rate from brucellosis in Iowa for the five-year prewar period 1935 to 1939 was 5.31 per 100,000. Due largely to increased pork and livestock production, the rate increased to 13.00 per 100,000 during the five years 1940 to 1944, corresponding in general to the period of World War II. The number of positive agglutination reports as notified from the State Hygienic Laboratory is considerably greater than that of officially reported cases. With complete reporting based on positive agglutination in diagnostic dilutions, rates per 100,000 might be nearly twice as high as here presented.

#### EPIDEMIOLOGIC FACTORS AND FINDINGS

*Age, Sex and Seasonal Prevalence.* Out of a total of 2,082 brucellosis case reports, completed through interest and courtesy of Iowa physicians during the twelve-year period 1933 to 1944, male patients numbered 1,639 and females 443, a male to female ratio of about five to one. Among patients under nine and over seventy years of age, the disease occurs as frequently in females as in males, indicating (1) equal susceptibility in the two sexes and (2) probable exposure through unpasteurized dairy products. The preponderance of males over females in the teen-age group and in the adult decades below seventy, emphasizes the major rôle played by direct contact in causing the marked difference in attack-rate in the two sexes. Although brucellosis is with us always, every month of the year, more cases have onset of symptoms in June, July and August (probably following con-

tact with animals during the farrowing and calving season) than in any other three-month period.

*Occupation and Residence.* Analysis of 1,378 case reports contributed by Iowa physicians during the five-year period 1939 to 1943, showed an average annual rate of fourteen cases per 100,000 population in the farm group, compared with nine cases per 100,000 in cities and towns under 2,500 and five cases per 100,000 in cities over 2,500, exclusive of packing house workers. (Table II.)

The specific rate among packing house employees for the same period was 245 per 100,000, about fifty times as high as the rate among urban residents who do not come into direct contact with livestock.

#### INFECTION CAUSED BY THE BOVINE ORGANISM, *BRUCELLA ABORTUS*

Discovery of *Brucella abortus* ("bovis" preferred by the late Prof. Wm. H. Holmes) as the usual causative agent of brucellosis in the cow, was announced by the veterinarian Bang in 1896. The first case of brucellosis of man or undulant fever with probable origin in the United States, was reported by Craig<sup>1</sup> in 1905. Schroeder and Cotton<sup>2</sup> in 1913 demonstrated the presence of this organism in the milk of cows infected with brucellosis or Bang's disease. Alice Evans,<sup>3</sup> recently retired as Senior Bacteriologist, U. S. Public Health Service, made a distinct contribution in 1918 in showing that there was no demonstrable difference between *brucella* as recovered from a patient and a culture of *Brucella abortus* from an infected cow. Miss Evans also stated that human illness might result from exposure to infection in animals. A case of brucellosis of man or undulant fever which occurred in Baltimore in 1922, was reported by Keefer.<sup>4</sup> Acken<sup>5</sup> reported a case from New York in 1926 and Carpenter

TABLE II

BRUCELLOSIS IN IOWA 1939-1943

Number of Cases in Urban and Rural Areas and Rates per 100,000 Population Based on 1,378 Case Reports Completed through Courtesy of Iowa Physicians

Rural Areas					Urban Areas				State Totals <sup>c</sup>	
Year	Farm Group <sup>a</sup>		Cities, Towns under 2500 <sup>b</sup>		Cities over 2500 <sup>d</sup>					
Farm Residents			All Others		Packing House Workers <sup>e</sup>		All Others		All Cases	
	No.	Rate per 100M	No.	Rate per 100M	No.	Spec. Morbid Rate	No.	Rate per 100M	No.	Rate per 100M
1939	80	8.7	37	6.9	19	95.0	37	3.4	173	6.8
1940	107	11.7	39	7.3	67	335.0	48	4.4	261	10.3
1941	135	14.7	37	6.9	35	175.0	59	5.4	266	10.5
1942	150	15.5	53	9.9	62	310.0	65	6.0	330	13.0
1943	181	19.7	68	12.7	54	270.0	45	4.2	348	13.7
Totals 1939-1943	653		234		237		254		1378	
Avg. ann. cases	131		47		47		51		276	
Avg. rate per 100M		14.3		8.7		245.0		4.7		10.9

<sup>a</sup> 916,768 rural, farm population—Census, 1940.  
<sup>b</sup> 537,269 rural, non-farm population—Census, 1940.  
<sup>c</sup> 20,000 packing house workers (estimated total).  
<sup>d</sup> 1,084,231 urban population—Census, 1940.  
<sup>e</sup> 2,538,268, total population—Census, 1940.

and Merrian<sup>6</sup> reported two more cases in that state in the same year. In Iowa, clinical diagnosis of the first case of brucellosis was made by Woodward<sup>7</sup> in December, 1926. Subsequent laboratory and epidemiological study of the disease in Iowa and the United States was made by Hardy<sup>8</sup> and associates.<sup>9</sup>

Brucellosis due to *Br. abortus* is usually of sporadic occurrence, regardless of whether illness results from unpasteurized dairy products or from direct contact with infected cows. It is highly probable that situations similar to that described in the

following paragraphs occur from time to time in communities throughout the country.

1. *Clinical Cases in Greenfield.* In September, 1942, and during July and August, 1943, three cases of brucellosis occurred in Greenfield (population 1,869), county seat of Adair County, Iowa. Those ill were C. W., fifty-two year old male patient of Wm. F. Crew, M.D.; P. C., fifty-six year old male and A. H., thirty-two year old male, patients attended by E. O. Reynolds, M.D. The diagnosis was made on the basis of symptomatology and the presence of agglutinins in diagnostic dilution (1:1280,

1:320 and 1:160, respectively) in the blood serum of these individuals. None of the patients had recently been in direct contact with farm animals but all had used raw milk as distributed by a local, the R dairy.

Since many families in the city had used the same milk as the three patients, an agglutination and skin test survey was carried out in February, 1944, in cooperation with local physicians, city and school officials, to obtain further information as to the extent of infection.

2. *Results of Agglutination Tests.* Agglutination tests were performed at the State Hygienic Laboratory on the blood serum of 232 persons (mostly children in upper grades, high school students and some adults). The serum of twenty-three individuals (10 per cent) showed positive agglutination in dilutions from 1:40 to 1:2560 as follows: seven in 1:40, five in 1:80, five in 1:160, four in 1:320, 1 in 1:1280 and 1 in 1:2560. Blood cultures were taken from six persons whose agglutination tests were positive in dilutions 1:160 and above; efforts to isolate *Br. abortus* through a period of a month of incubation and transfer of cultures were unsuccessful.

3. *Latent, Subclinical Infection.* Of the group of twenty-three persons with positive agglutination as listed, two married women, thirty-one and thirty-five years of age respectively and a school girl, age eleven, gave the history of recent mild illness not previously recognized as brucellosis, lasting several weeks and characterized by fever, chills or chilliness, loss of weight, tired feeling and in the case of the child, also night sweats and pallor. The other twenty were apparently well, showing evidence of latent infection but without clinical manifestations. None of the twenty has since been reported as having suffered illness.

4. *Results of Intradermal Tests.* Intradermal tests were administered with brucel-

lergen\* using 0.1 cc. of a 1:12,000 dilution. Among 248 tested, 48 or 20 per cent showed positive reaction in forty-eight hours, with erythema and edema varying from 15 to 90 mm. in diameter. Of 114 persons having used milk from the R dairy (suspected as the source of infection), 25 or 22 per cent had positive skin tests. Of 134 individuals using milk from their own cows or other sources, 23 or 16 per cent showed positive skin reactions. The fact that 16 per cent of apparently normal individuals in the survey showed an allergic response following the use of brucellergen, is evidence of the unreliability of the intradermal test alone, to establish a clinical diagnosis of brucellosis.

5. *Isolation of Brucella from Milk.* Cream from the R dairy was inoculated into two guinea pigs March 2, 1944, at the State Hygienic Laboratory. On April 17th, the spleen and liver of these animals as reported by one of the authors (I. H. B.), were two to three times normal size and irregularly roughened by 1 to 3 mm. abscesses or granulomata. Serum of the guinea pigs agglutinated brucella antigen (1:640 and 1:1280) and *Br. abortus* was isolated from the organs of both.

6. *Milk Now Pasteurized.* It should be added that through efforts of the milk sanitarian of the State Department of Health and of informed city officials, together with results of the survey, two pasteurizing plants were promptly installed.

#### INFECTION CAUSED BY THE PORCINE ORGANISM, BRUCELLA SUIIS

*Br. suis* was first isolated from fetuses of infected swine by the veterinarian Traum, in 1914.

*Infection Resulting from Direct Contact.* Former field investigation of brucellosis cases in Iowa in cooperation with attending

\*Furnished through courtesy of Michigan State College by I. Forest Huddleson, D. V. M.

physicians and the United States Public Health Service, revealed that many of the patients gave the history prior to illness, of using dairy products only sparingly, but of having had direct contact with hogs; some of the sows had lost litters and were later found to react to the agglutination test for brucellosis. Blood cultures from a number of the patients yielded a strain of brucella that proved, when tested by Huddleson's<sup>10</sup> dye-method of differentiation, to be *Brucella suis*.

As suggested by Hardy,<sup>11</sup> direct contact with hogs must be considered a major factor to account for the relatively high incidence of brucellosis in the midwestern states of this country (see rates per 100,000 in Table 1). Cases resulting from direct contact, whether with infected hogs or cows, are usually of sporadic and accidental occurrence; such instances in the aggregate, probably exceed in number those traceable to contaminated dairy products. Cases of brucellosis affecting farm workers result from varied sources of infection on individual farms. The extent of brucella infection is more readily determined in the meat packing industry where many are exposed to an enormous concentration of animals, some of which are known to harbor brucella. Surveys conducted in Iowa in past years have shown the incidence of active and latent infection among apparently healthy workers as determined by positive agglutination reactions (1:40 or above), on one occasion to be 18.2 per cent (240 tested)<sup>12</sup> and 10.8 per cent of 251 tested at a later time.<sup>13</sup>

The importance of swine brucellosis is demonstrated in a report by McNutt<sup>14</sup> who examined 1,547 hogs by the rapid agglutination method and found 3 per cent of the animals infected. He isolated *Br. suis* from 14 or 41 per cent of thirty-four reacting animals; organisms were cultured from the spleen, liver, uterus and lymph nodes.

*Infection Resulting from Unpasteurized Dairy Products.* From time to time, a raw milk supply becomes contaminated with *Br. suis*, brought about by hogs sharing the same lot with dairy cows. When infection is transmitted from infected hogs to the udder of one or more dairy cows, multiple cases of brucellosis are certain to result, probably because *Br. suis* is more invasive, prone to produce a more severe infection than that from *Br. abortus*. Three epidemics of this nature have been investigated in Iowa under auspices of the State Department of Health during the past thirteen years. Report of the first epidemic was made by Beattie and Rice,<sup>15</sup> of the second by Borts and associates.<sup>16</sup> Clinical and epidemiologic findings in a third outbreak, are summarized as follows:

1. *Multiple Clinical Cases in Bennett.* During November, December and January, 1942 and 1943, an outbreak of brucellosis caused by *Br. suis* occurred at Bennett (population 352), Cedar County, Iowa. Six cases of the disease were diagnosed by local physicians, based on positive agglutination reactions on blood serum, ranging from 1:320 to 1:1280. In February, 1943, an agglutination and skin test survey was carried out at Bennett, in cooperation with school and town officials, L. E. Bees, M.D., A. R. Stephenson, D.V.M. and D. M. Harris, M.D., then Director of District Health Service No. 8.

2. *Results of Agglutination Tests; Latent Infection.* Agglutination tests were performed on the serum of 119, mostly consolidated school students but including some adults in the community. Twelve persons (10 per cent) showed positive agglutination in dilutions 1:40 to 1:2560 as follows: two in 1:40, five in 1:160, one in 1:320, three in 1:640 and one in 1:2560. Of the twelve, one boy had missed school several days due to a "cold," with cough and slight fever. The remaining eleven gave

no history of illness, showing latent infection without clinical symptoms. Three of the children with latent infection likewise had a bacteremia, *Br. suis* being isolated from blood cultures. None of the eleven has been reported as having illness caused by brucellosis since the time of the survey.

3. *Results of Skin Tests.* Skin tests were performed on 112 persons, with brucellergen furnished through courtesy of Dr. I. F. Huddleson, D.V.M., of Michigan State College. Among fifty-one who had used contaminated milk from the M dairy (*Br. suis* was isolated from the milk), 24 or 47 per cent showed erythema and edema in forty-eight hours. Out of sixty-one using milk from their own cows or from other sources, 15 or 25 per cent showed positive skin reactions. Eleven of the twelve with positive agglutination findings also showed allergic response to brucellergen.

#### INFECTION CAUSED BY THE CAPRINE STRAIN, *BRUCELLA MELITENSIS*

It was the British physician, David Bruce,<sup>17</sup> who in 1887 was the first to isolate the causative organism from the blood of patients on the island of Malta who suffered from a febrile disease known as Mediterranean or Malta fever. All cases were traced to goats as the source of infection. In 1911, patients of the same disease in Texas and likewise with source in goats, were investigated and reported by Ferenbaugh,<sup>18</sup> and Gentry and Ferenbaugh.<sup>19</sup> Yount and Looney<sup>20</sup> in 1912 reported five patients with Brucellosis melitensis in Arizona and in 1922 Lake<sup>21</sup> diagnosed and reported thirty-five cases of this type of the disease in the same state. In 1935, Meyer and Eddie<sup>22</sup> reported results of a survey of *Br. melitensis* infection in goats in the southwest. Evans<sup>23</sup> in 1937 reported the distribution of *Br. melitensis* in the United States, including recognition of human cases in Texas, North Carolina and Kansas. Of 150

strains of *Brucella* isolated from patients hospitalized at General Hospital, Mexico City (1938 to 1941) and reported by Castaneda, Tovar and Velez<sup>24</sup> in 1942, strains numbering 143 (95 per cent) were *Br. melitensis*.

*Br. suis* and *Br. abortus* were for years believed to be the only two species of brucella to occur in Iowa. Although *Br. melitensis* was isolated from the blood of a patient hospitalized in Iowa in 1930,<sup>25</sup> the man was a Mexican and the melitensis infection was apparently acquired in Mexico, since onset of illness developed but a few days after the patient had left his native country.

*Br. melitensis* is now known to be endemic in Iowa. Between December, 1943 and July, 1946, the melitensis strain was recovered from the blood of forty patients in Iowa. Since July, 1944, one of the authors (I. H. B.)<sup>26</sup> has employed a tryptose broth medium (with technic modified from that of Bohls and Schuhardt), which renders possible the isolation of brucella strains not alone from blood cultures but also from the blood clot contained in the specimen (aseptic precautions essential) which the physician forwards to the laboratory for the agglutination test.

In a series of twenty *Br. melitensis* cases investigated in Iowa during 1945, ten were packing house workers; the remaining ten were farm workers or visitors on farms. Only seven of the twenty patients had been in contact with sheep preceding illness, and none with goats. Twelve, or 60 per cent of the patients were in direct contact with hogs only, prior to onset of illness gave no history of contact with sheep. Recovery of *Br. melitensis* from tissues of hogs taken from a farm in Iowa has recently been reported by Jordan, Borts and McNutt.<sup>27</sup> Milk cows on the farm concerned failed to react to the brucella agglutination tests and brucella was not isolated from the milk following cultural and guinea pig inoculation.

In April 1946, McNutt isolated another strain of *Br. melitensis* from tissues of a hog belonging to a farmer whose wife developed brucellosis. Shortly before onset of symptoms, the patient had handled newborn pigs. Her serum showed (1:1280) agglutination and the blood clot yielded *Br. melitensis*.

#### ISOLATION OF BRUCELLA FROM PATIENTS

During the period from September, 1927 to December 1, 1945, brucella strains totaling 358 were isolated at the State Hygienic Laboratory from the blood and tissues of brucellosis patients in Iowa. Of these strains, 238 (66 per cent) were *Br. suis*, 88 (25 per cent) were *Br. abortus* and 32 (9 per cent) were *Br. melitensis*.

Damon,<sup>28</sup> former Director of Laboratories, Alabama State Department of Health recovered ninety-one brucella strains during the five-year period 1939 to 1943. Sixty-nine (76 per cent) of the strains were *Br. suis*, twenty-one (23 per cent) *Br. abortus* and one (1 per cent) untyped.

Similarity in blood culture findings as compiled in Alabama and Iowa serves to emphasize the importance of hogs as a relatively frequent source of human infection not only in the corn belt but also in the South.

*Pathology.* Mortality from brucellosis as a direct cause of death does not usually exceed 2 or 3 per cent. Forbus<sup>29</sup> describes the pathological findings in three types of brucellosis: (1) acute, septicemic, (2) subacute, focal or localized and (3) chronic lymphogranulomatous.

According to Forbus: "The septicemic case shows little that is specific of brucella infection; the findings are those of almost any bacteremia with pronounced intoxication." Infection now and then becomes localized to cause vegetative endocarditis, orchitis, osteitis, meningitis or subacute arthritis.

The chronic lymphogranulomatous form

of brucellosis is characterized by enlargement and lymph nodes. Forbus presents an excellent detailed portrayal of the gross and microscopic appearance of lesions. He states: "The basic reaction is a progressive proliferation of the large monuclear cells of the reticuloendothelial system accompanied by the exudation of fibrin and sometimes by hemorrhage. This is followed by coagulative necrosis—and finally, by the proliferation of fibroblasts or the formation of a dense scar composed of reticulum."

Pathological findings in an Iowa case complicated by meningoencephalitis were reported by Hansmann and Schenken.<sup>30</sup> DeGowin and Borts<sup>31</sup> recently reported postmortem findings on a patient who developed vegetative endocarditis and a mycotic aneurysm of the femoral artery.

*Symptomatology.* The patient with clinical signs of brucellosis may have several or all of the following: fever, chills, sweating, weakness, malaise, headache, joint pains, backache, anorexia and loss of weight. These ten symptoms and signs are listed in the order of frequency of mention on 1,011 case reports completed by Iowa physicians.

Bierring,<sup>32</sup> in an analysis of 150 cases of brucellosis and based on his own experience with the disease, presents the following clinical picture:

"Emphasis should be placed on the character of the onset, the rigors, the chills with profuse sweating, the muscular and joint pains, the loss of weight, and the continued and persistent character of the fever curve.

"The usual onset is gradual and insidious in the development of noticeable weakness with accompanying tired feeling. The patient often seems quite fresh in the morning but by the latter part of the afternoon is so fatigued as to be hardly able to get about. A headache and backache of greater or lesser severity are often features of the onset. Likewise, loss of appetite, digestive distress and constipation are frequent early symp-

toms. After a few days, or possibly several weeks, the patient becomes conscious of a hot feeling mostly in the afternoon, and is usually surprised to learn that the temperature is above normal. A feeling of feverishness, and light rigors, and chills, are often first indications of fever. Again, the onset may be ushered in abruptly by a severe chill and rapid rise of temperature, followed by very profuse sweating, and this, with the general muscular pains, gives the impression of a profound infection."

#### FOLLOW-UP OF PATIENTS ILL IN 1943 AND 1942

In May, 1946, a letter and follow-up form were forwarded to physicians of Iowa to secure information regarding the duration of illness and present condition of patients whose blood serum in 1943, (several had onset of illness in 1942) showed positive agglutination in dilutions ranging from 1:40 to 1:2560, as notified from the State Hygienic Laboratory of the Iowa State Department of Health.

1. *Duration of Illness.* Among 114 patients for whom replies were received from more than 100 attending physicians, four deaths occurred in which brucellosis was the primary or contributory cause (3.5 per cent mortality). Duration of illness in fifty-four (47 per cent) was within three months; in sixty-eight (60 per cent), within five months and in eighty-seven (76 per cent) within one year. Eight patients (7 per cent), had symptoms lasting more than a year, twelve (10.5 per cent) were ill over two years and one patient longer than four years. Six reports did not indicate the duration of illness.

2. *State of Health in May, 1946.* In the series of 114 patients under consideration, sixty-five or 57 per cent were stated as being "well as ever"; the health of thirty others (26 per cent) was "fair." Not all of the reports were complete, some of the patients having changed location (including several

who served in World War II), rendering follow-up unsatisfactory.

Considering separately fifteen of the twenty patients in this series whose illness lasted a year or longer, seven of these were stated as being "well as ever in May 1946," the condition of seven was "fair," while the health of but one was "poor." Current complaints of eight of these patients who are known to have had acute brucellosis three or four years ago and some of whom may now be regarded with a degree of certainty as showing residual effects of the disease (chronic brucellosis) include the following: weakness, inability to do a day's work, occasional fever of moderate grade, night sweats, pains in muscles.

#### DIAGNOSIS AND LABORATORY AIDS

A diagnosis of brucellosis based entirely on clinical manifestations cannot be made with accuracy; certain laboratory procedures are essential to confirm the clinical findings.

1. *Isolation of Brucella.* The recovery of brucella from the blood of a patient whose symptoms suggest brucellosis, establishes the diagnosis beyond a doubt. The isolation of brucella not only confirms the clinical diagnosis, but also makes possible identification of the species of organism through resort to Huddleson's dye-method of differentiation, and thereby aids greatly in the tracing of infection to its source in the hog, cow, sheep or goat.

There are physicians who would limit the diagnosis of clinical brucellosis to patients who show a positive blood culture. Although it is likely that bacteremia is present during the early febrile period in the majority of all acute brucellosis cases, brucella is actually isolated from a relatively small percentage due to factors such as the following: (1) failure to secure blood cultures during the early febrile stage of the disease; (2) failure to use media adapted



for growth of brucella; (3) lack of facilities for incubating cultures under CO<sub>2</sub> and (4) discarding of cultures after a few days of incubation. Insistence on positive blood culture as the sole criterion to confirm clinical diagnosis causes many cases of brucellosis to be missed or overlooked.

2. *The Agglutination Test.* This laboratory procedure is next in importance to the blood culture as a confirmatory diagnostic aid. Brucellosis reports as notified officially in most if not all of the forty-eight states are, so far as known, based primarily on positive agglutination findings to confirm the physician's clinical diagnosis.

Both rapid and slow methods of agglutination are trustworthy. When negative at first, agglutination tests should be repeated at weekly or ten day intervals. Although a negative test does not exclude the disease, agglutinins in diagnostic dilution (1:40, 1:80 or higher) are apt to be present at one time or another in as high as 90 per cent of all cases showing early clinical manifestations.

The agglutination titer tends to decrease during the months following acute illness, and usually becomes entirely negative. On the other hand, brucella agglutinins in diagnostic dilution are known to persist for several years in the serum of some patients, even as long as ten years after apparent clinical recovery.

3. *The Skin Test.* A positive skin test with brucellergen or other brucella antigen connotes an allergic response which, like a positive Mantoux or tuberculin reaction, probably means that exposure to infection has occurred either recently or at some time in the past. A positive intradermal test in the absence of positive blood cultures or positive agglutination reactions does not warrant the conclusion that the symptoms of which the patient complains are due to brucellosis. Surveys in Iowa have revealed positive skin tests in from 10 to 25 per cent of apparently healthy persons. The authors

agree with Goodman<sup>33</sup> that clinical brucellosis is ordinarily of sporadic occurrence and that reliance on a positive skin test to confirm the clinical impression leads very often to uncertainty if not to error in diagnosis.

4. *The Opsono-Cytophagic Test.* Experience of various workers with the opsonocytophagic test and interpretation of results have been summarized by Huddleson.<sup>10</sup> There is need for further study to determine the value of this method as a laboratory aid in clinical diagnosis.

5. *Need for Additional Diagnostic Aids.* According to Alice Evans,<sup>34</sup> the most reliable indicator of infection, apart from the recovery of brucella, is a positive agglutination reaction in dilution of 1:40 or higher. Miss Evans states that "there is great need for further perfection of methods for the diagnosis of chronic brucellosis."

#### TREATMENT—PROPHYLAXIS

An Iowa physician epitomized his own experience with treatment of brucellosis by stating that while one patient tended to improve rapidly under any method of care, another failed to respond no matter what therapeutic measures were applied.

Early diagnosis of the acute case and confinement of the patient to bed or complete rest until ten days to two weeks after the temperature has become normal are of paramount importance. Rest, preferably in bed, should be supplemented by encouragement of the patient, a high caloric diet, forcing of fluids, control of constipation and other symptomatic care as may be required. Faithful adherence to the complete rest regimen is apt to be rewarded by decrease in duration of illness, also by lessened likelihood of complication, recurrence of symptoms and chronicity.

Simpson<sup>35</sup> and Harris<sup>36</sup> give detailed consideration to the management of this disease.

Some patients react favorably to use of brucellin or to non-specific protein therapy. Penicillin and sulfatherapy in combination, are frequently though not always effective; the former may prove life-saving should the patient's lowered resistance render him vulnerable to secondary infection (e.g., streptococcal pharyngitis). An Iowa physician, meticulous in the keeping of hospital records and in securing repeated blood cultures as a means of appraising therapy, has noted excellent results clinically in three patients following the use of streptomycin.

When illness from brucellosis is prolonged, this may be due to localization of infection. Such localization is now and then amenable to treatment. An Iowa boy, aged nine, had symptoms lasting over two years, including repeated attacks of tonsillitis; remarkably prompt recovery of strength was noted following tonsillectomy. Another patient improved rapidly after removal of an ovarian cyst, fluid content of which yielded a pure culture of *Brucella suis*. A third patient developed osteomyelitis of the second and third lumbar vertebrae, which apparently healed under orthopedic care. Strongly positive agglutination reactions led to diagnosis of brucellosis in these cases.

Decrease in the prevalence of brucellosis of man depends upon collaboration with official agencies and the veterinary medical profession in measures designed to drain the reservoir of infection in animals. Such measures include: (1) discovery and control of sources of infection in hogs and cows, sheep and goats; (2) reducing to a minimum the hazard of direct contact with animals; (3) improved sanitation on farms and in the packing industry; (4) active immunization of animals (calfhood vaccination) and (5) careful supervision and pasteurization of all dairy products.

There is urgent need for evaluation of a vaccine similar to that used by Kolmer and

associates,<sup>37</sup> for active immunization of individuals whose occupation entails daily exposure to brucella infection.

#### COMMENT

Infection caused by brucella organisms is always more widespread in a community than is indicated by the occurrence of active clinical cases. Information as to the extent of infection is obtainable through agglutination and skin test surveys carried out among groups of individuals subject to exposure through direct contact with brucellosis in animals or through use of unpasteurized milk from infected dairy cows. Results of recent surveys as here presented confirm those of a previous report.<sup>12</sup> Survey findings indicate that the ratio of latent or sub-clinical to clinical cases of brucellosis may be 8:1 or higher. The incidence of latent infection, as demonstrated by positive agglutination reactions and also by positive blood cultures, appears to be an important factor to explain or account for the usually sporadic occurrence of clinical cases.

The late Wade Hampton Frost<sup>31</sup> was the first to demonstrate clearly the inter-relationship between infection, immunity and disease in the epidemiology of diphtheria and poliomyelitis. It seems evident that the principles enunciated by Frost also hold true for brucellosis.

The practice of diagnosing brucellosis, acute or chronic, on the basis of no more than a positive skin reaction is (1) often inaccurate, (2) tends to bring the matter of diagnosis of the disease into disrepute among physicians who rely on positive blood cultures and positive agglutination findings and (3) multiplies by many times the actual occurrence of clinical brucellosis.

#### SUMMARY AND CONCLUSIONS

1. Information is presented pertaining to epidemiologic, clinical and laboratory

aspects of brucellosis of man as caused by the three species of brucella.

2. In addition to the porcine and bovine varieties, the caprine strain (*Br. melitensis*) is now known to be endemic in Iowa; thus far hogs (not sheep or goats) have proved to be the source of infection and *Br. melitensis* has been isolated from swine tissues.

3. Agglutination and skin test surveys help to reveal the extent of brucella infection in families or groups and the role played by latent infection in association with clinical cases of the disease.

4. Recovery of brucella and positive agglutination reactions in diagnostic dilution (1:80 and above) are two laboratory mainstays to confirm the clinical diagnosis.

5. A positive intradermal test should under no circumstances be used as a sole basis to confirm the clinical impression of acute or chronic brucellosis.

6. Prevention of human illness from this disease is dependent upon control and eradication of the disease in animals which serve as the source of infection; upon reduction to a minimum of direct contact with animals and their tissues and upon thorough pasteurization of all dairy products.

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# Seminars on Rheumatic Fever

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## The Relationship of Streptococcal Infections to Rheumatic Fever\*

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IN order to evaluate the evidence which indicates a close relationship between rheumatic fever and infections with hemolytic streptococci, it is advisable to have a clear picture of our current knowledge of these microorganisms, and also of certain immunological reactions in which they take part.

The streptococci comprise a large class of bacteria which grow as round or oval forms in chains of various lengths. In addition to pathogenic varieties, there are many which are not pathogens, some of which play a useful industrial role; for example, in the ripening of certain cheeses. Others may serve as test objects for the detection of biological or chemical products. In the earlier years of bacteriology, classification techniques were based largely upon the ability of the respective strains to grow in or on various artificial media or to split certain chemical agents; and today some of these characteristics are still valuable aids in studying some streptococci.

Another method of classification consisted in applying the name derived from the pathological condition from which they were isolated; i.e., *Streptococcus pyogenes* from purulent conditions, or *Streptococcus erysipclatis* from erysipelas. It is now clear that either purulent or erysipclatous conditions can be induced by the same strain of

streptococci as well as by strains belonging to different immunological groups or types; hence this system of classification has little validity.

Still another, and relatively useful appellation, derives from the action of streptococci on red blood cells. If, when grown in or on media containing intact erythrocytes, the hemoglobin is changed to methemoglobin and the majority of the blood cells remain intact, the designation green or viridans is employed; if the hemoglobin is released from the red cells and not changed to methemoglobin, the streptococci are termed hemolytic; if the red cells and their contents are not visibly affected, the streptococci are designated as indifferent. The three Greek letters alpha, beta and gamma have also been used to describe these three classes of streptococci.<sup>1</sup>

The most modern, and in many respects the most useful system of classification, is based on immunological procedures which doubtless stem from the chemical characteristics of various streptococcal components. This immunological classification was developed by Dr. Griffith<sup>2</sup> in England, but more completely by Dr. R. C. Lancefield<sup>3</sup> in this country.

Streptococci are divided immunologically first into groups, and then the members of

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For description of methods of grouping and typing, see appendix at the end of this lecture, page 182.

certain groups are further subdivided into types.

*Group Specificity.* In 1924, Hitchcock<sup>4</sup> found that hemolytic streptococci, isolated from a wide variety of human diseases, possessed in common a serologically active carbohydrate which was designated as C substance. This fraction C was found to react specifically with the serum of animals immunized with any strain of hemolytic streptococci subsequently shown to belong to so-called group A, and failed to react with serum of animals immunized with a series of strains isolated from lower animals. Subsequently Lancefield<sup>5</sup> showed that another group-specific carbohydrate substance was present in streptococci isolated from many cases of bovine mastitis; and thus a new group, B, was discovered. Eventually, several other groups were recognized, the most characteristic sources of which are set out in Table I.

TABLE I  
MOST CHARACTERISTIC SOURCE OF VARIOUS GROUPS OF  
STREPTOCOCCI (LANCIEFIELD)

GROUP	MOST CHARACTERISTIC SOURCE
A.....	Man
B.....	Bovine mastitis
C.....	Most streptococcal animal diseases
D.....	Cheese; enterococci and other human saprophytes
E.....	Normal milk
F.....	"Minute"
G.....	"Minute" and large
H.....	} Man: nasopharynx, usually nonpathogenic
K.....	
L.....	
M.....	
M.....	} Dog

While the primary sources shown in Table I represent the environment in which the respective members of the several groups usually occur, they may also find conditions suitable for their growth in other environments where they may even be pathogenic. These usual and unusual distributions of streptococcal groups are shown in Table II.

These facts are of more than mere academic interest. While members of group A are responsible for most streptococcal dis-

eases in man, members of several other groups have been isolated from various parts of the human body, where occasionally they possess disease-inducing capacities.

TABLE II  
PATHOGENICITY OF SEROLOGIC GROUPS OF HEMOLYTIC  
STREPTOCOCCI

Animal species	Streptococcal groups		
	Chief pathogens	Usually saprophytes, occasionally pathogens	Saprophytes (apparently)
Man.....	A	B, C, D, F, G, H	K, L
Monkey....		A, G	C
Cattle.....	B, C	A, G	D, E, H, L
Horse.....	C		
Dog.....	G, L, M		C
Chicken....	C.....	A (?)	G
Swine.....		E, L	
Goat.....			
Sheep.....			
Fox.....		M	
Ferret.....			
Rabbit....		A, B	
Guinea pig.			
Mouse.....		A, B, C	

Again, the milk coming from cows having mastitis due to streptococci belonging to groups B or C can be used for human consumption with relative impunity. When, on the other hand, as occasionally happens, a cow develops mastitis due to group A streptococci, her milk is a grave menace; and the distribution of such contaminated milk has lead to many epidemics of septic sore throat. Incidentally, such epidemics are often followed shortly by epidemics of rheumatic fever.<sup>6</sup> In contrast, it should be noted that human infections with streptococci belonging to groups other than A have not been shown to induce rheumatic fever.

An experimental predicament that arises from the normal distribution of the various groups among the several animal species is the difficulty of infecting an animal artificially with groups to which that species is

not usually susceptible, at least not to the extent encountered when the microorganisms operate in their "normal habitat." This makes analogies derived from animal experiments difficult of interpretation when applied to human maladies.

While the carbohydrate C fraction is useful in grouping streptococci, other biological phenomena depending upon its existence are not known. There is no group-specific agglutination; and the amount of group-specific C antibodies present in a given serum does not bear any relationship to such non-type-specific agglutinating capacity as that serum may possess. While the C substance is fairly constant in amount in a given strain, variations in the amounts of this substance seems to have no direct bearing on the virulence of the respective microorganism. This C carbohydrate forms part of the streptococcal cell from which it can be separated by complete disintegration of that cell. When so separated, it is non-toxic for animals.

*Types among Group A Streptococci.* The strains of streptococci comprising group A are further divisible into immunological types on the basis of their content of two different type-specific components, the so-called M and T substances.<sup>7</sup>

1. *Type-Specific Protein M.* This antigen is found in the variants of group A streptococci which form mucoid or matt colonies on solid media.<sup>8</sup> It apparently is mainly situated near the surface of the streptococcal cell. It is readily destroyed by certain proteolytic enzymes and by strong alkalies, but resists the action of fairly strong HCl. This property renders it extractable from the cell with HCl, and allows of further partial purification. Such extracts form type-specific precipitates when mixed with the properly absorbed sera of rabbits which have been hyperimmunized with the homologous strains; and such reactions are utilized in the precipitin typing technics.<sup>9,10</sup> By ap-

plying this technic, over forty different types have been identified and there are probably many others still not identified.

Certain strains of a given type will also agglutinate type specifically with homologous immune sera; and on this basis Griffith<sup>11</sup> developed a slide agglutination technic for identifying several types; but this technic sometimes leads to confusing results due to the presence in the streptococcal cell of other immunologically reactive components.

2. *Type-Specific T Substance.* A second type-specific component, the T substance, was also discovered by Lancefield.<sup>12</sup> It is destroyed by strong acids, but resists the proteolytic action of such enzymes as trypsin or pepsin. It is a strong agglutinin. While certain strains have M and T substances both belonging to the same type, among strains belonging to certain other types there are T agglutinogens which are common to several types. Two such series have been described:<sup>13</sup> One comprising types 4, 24, 26, 28, 29 and 46 have closely related T substances but type-specific M antigens; and a second series comprising types 15, 17, 19, 23, 30 and 47 contain another common immunologically distinct T substance. These T substances shared in common by several types make it impossible to distinguish by agglutination tests a member of one of these series from another belonging to the same series. One other peculiarity among certain types has been described: Types 10 and 12<sup>14</sup> possess common M antigens but immunologically distinct T agglutinogens.

In animals artificially infected, type-specificity with respect to immunological protection runs parallel to the specificity as determined by M anti-M precipitin reactions, and not by T anti-T agglutination unless the M and T antigens of a given strain belong to the same type. The passive protecting capacity of a given type-immune serum also closely parallels its anti-M con-

tent; but no similar protective relationship has been demonstrated with respect to the T antigens and their corresponding antibodies in a given serum. Furthermore, humans or animals<sup>15</sup> infected with group A streptococci of a given type are resistant for fairly long periods to reinfection with that type, but are readily infected with strains of heterologous types. This fact has important epidemiological connotations.

3. *P Substance.* Other substances which can be extracted from the bodies of streptococcal cells are the P antigens. They probably comprise a mixture of nucleoproteins, which have neither group nor type specificity. In fact, similar substances are extractable from other cocci and bacilli. It is difficult to remove some of them completely from extracts containing M and T antigens; and this fact makes it somewhat hazardous to interpret immunological tests, both *in vivo* and *in vitro*, when reagents are employed containing mixtures of type-specific components, M or T, and non-specific nucleoproteins.

The four classes of substances above discussed are all apparently a part of the group A streptococcal cell. The three components C, T and P are usually fairly constant in any given strain, although occasionally either the C or T antigens may disappear from a strain which retains all of its other antigenic components.<sup>16</sup> The M antigenic content of a given strain is, on the other hand, quite variable. Highly virulent variants produce large amounts of M, lowly virulent variants little or none. By serial animal passage a strain of low virulence and with poor M-producing capacity can often be made highly virulent with a correspondingly large M content. Strains isolated from the nasopharynxes of patients who have carried them for a long time, so-called "carrier strains," usually elaborate only small amounts of M antigen or even none. Such strains often grow in "glossy" colonies on

blood agar, and must be identified immunologically by means of anti-T agglutination reactions because their low content of M makes it impossible to extract enough for a precipitin test, while their more stable T content makes them agglutinable. Such glossy carrier strains have little virulence, and probably little invasive capacity.<sup>17</sup>

The only type-specific antibody which it has so far been possible to demonstrate *in vitro* in human sera, which is not complicated by cross reactions, is the so-called bacteriostatic antibody.<sup>18</sup> The presence of this antibody is shown by the phagocytosis of virulent M-producing strains of streptococci. This phagocytosis by normal leukocytes is effectuated by three components: complement; a thermostable factor; and an antibody which is type specific with respect to M antigens and not to T antigens. Application of bacteriostatic tests has demonstrated the development of type-specific antibodies in the blood of patients following group A streptococcal infections,<sup>18,19</sup> and as might be expected, in that of patients with rheumatic fever. The difficulties repeatedly encountered in searching for type-specific antibodies with agglutination, precipitin, and complement-fixation technics probably stem in large part from the great difficulty in preparing antigens used in these technics in a pure form, free from other immunochemical components which give cross reactions with the various antibodies which inevitably occur in the sera of animals or humans infected with microorganisms containing a variety of such components.

*Extracellular Streptococcal Products.* In addition to the substances contained within the bacterial cell, group A hemolytic streptococci elaborate soluble substances into the media in which they have been grown; and antibodies reacting with some of these substances have been described. The following soluble products have been fairly well studied:



1. *Streptolysins (hemolysins)*. The reagents responsible for hemolysis of erythrocytes are elaborated into the broth or blood agar. Todd<sup>20,21</sup> has described two: (a) Streptolysin O, which is oxygen labile, and while produced chiefly by most hemolytic members of group A, it is also produced by some strains of other groups; (b) streptolysin S, which is oxygen stabile and which seems to be peculiar to group A streptococci. Animals immunized with the soluble streptolysin O produce an antibody which combines with this lysin and thus inhibits its hemolytic activity. Similarly, antistreptolysin O appears both in the blood of animals and in that of about 90 per cent of human patients following group A streptococcal infections. In man, the amount of this antibody formed is very roughly proportional to the intensity and duration of the streptococcal infection. Todd<sup>22</sup> has further shown that certain strains of group A streptococci do not elaborate streptolysin O, but that their hemolytic capacity is due to other streptolysins. Persons infected with such streptococci naturally would not develop any antistreptolysin O; and it seems reasonable to conclude that at times the impossibility of demonstrating this antibody in the serum of patients is due to infections induced by these peculiar strains. It has been repeatedly shown that about 90 per cent of patients suffering from acute rheumatic fever have pathological amounts of antistreptolysin O in their serum. Such findings are strong evidence for predicting a close relationship between rheumatic fever and streptococcal infections. It should be emphasized, however, that the abnormal antistreptolysin O titre is not pathognomonic of rheumatic fever but of the precursory streptococcal infection.

Todd, Coburn, and Hill<sup>23</sup> have reported that during attacks of rheumatic fever patients have a lower average content of

antistreptolysin S in their sera than occurs in streptococcal infections without rheumatic fever sequelae. Weld<sup>24</sup> has described a very potent poison with hemolytic and other cytotoxic properties which is extractable from streptococcal cells. It apparently is the same as streptolysin S.<sup>25</sup>

2. *Fibrinolysin*. Many members of group A and some of groups C and G elaborate into broth in which they have grown a substance which appears to dissolve fibrin.<sup>26</sup> Christensen<sup>27</sup> has recently demonstrated that the lytic system consists of a zymogen normally present in human serum, and which remains inactive until it is combined with an activator, fibrinolysin\*, which is produced by the streptococci. In the serum of many patients suffering from streptococcal infections there develops an antibody, antifibrinolysin, which apparently neutralizes this activator, and thus prevents it from combining with the fibrinolytic proenzyme. The observation that most patients with rheumatic fever develop relatively large amounts of this antifibrinolysin in their serum, which normally contains little or none, is additional evidence that they suffer from the effects of a streptococcal infection.

3. *Erythrogenic Toxin*. This toxin, which is formed in broth by many group A streptococcal strains, by an occasional group C strain, and apparently by a very rare *Staphylococcus aureus*, appears responsible for the rash of scarlet fever.<sup>28,29</sup> It is neutralized by antierythrogenic antibody which appears in the blood of scarlet fever patients with recovery. Similar neutralizing antibodies are demonstrable in the sera of many persons with no history of scarlet fever, but who have probably suffered previously from mild or subclinical infections with streptococci having weak erythrogenic-toxin forming capacity.

It is now generally conceded that the difference in the clinical picture between

\* This has been designated as streptokinase.

two persons infected with an erythrogenic-toxin producing strain, one of whom develops scarlet fever and the other a simple nasopharyngitis, is that the second had in his serum antibodies against the erythrogenic toxin while the first did not. Because the rash-free patient usually has fever, malaise, and other general signs of intoxication, it appears logical to conclude that the streptococci elaborate other toxins, the nature of which is not well defined.

From the standpoint of inducing rheumatic fever, streptococcal infections, with or without a rash, have similar significance. Postscarlatinal rheumatism has been long recognized and its relationship to rheumatic fever has been the subject of many polemics.<sup>30</sup> The advantage of using scarlet fever as an example of precursory streptococcal infection lies in its clear-cut clinical peculiarities, and in the fact that it has long been a reportable disease, from which fairly reliable statistical analyses may be reconstructed.

4. *Hyaluronic Acid*. This substance is present in the capsular substance of streptococci, especially members of groups A and C, whence it readily diffuses into the surrounding broth. Some observers suggest that it is responsible for the virulence of group A streptococci,<sup>31</sup> and that in this respect it resembles the capsules of pneumococci. There is, however, quite convincing evidence that virulence of these streptococci is more closely related to their type-specific protein M content.<sup>32,33</sup> Hyaluronic acid is one of the principal components of the umbilical cord, synovial fluid, and the ground substance of connective tissue. As might be expected from its widespread distribution in the animal body, antibodies against hyaluronic acid have not been demonstrated. Whether hyaluronic acid, or a compound of which it is a component, has any pathogenic significance with respect to rheumatic fever is still an open question.

#### CASE REPORTS

In order to set forth the evidence of the close relationship between group A hemolytic streptococcal infections and rheumatic fever, case reports of four patients are presented. These illustrate various clinical courses in which there were different manifestations indicating the probable, possible, or questionable existence of rheumatic fever. On the charts are shown the evidence of streptococcal infections and the antibody responses to those infections. In all instances the streptococcal infection was scarlet fever; but we have seen many instances where simple tonsillitis or streptococcal nasopharyngitis played a similar role.

CASE I. This patient had a typical scarlet fever with type 19 streptococci in the nose and throat. Following a course of sulfadiazine, this strain apparently disappeared and was replaced by type 6, which in turn was replaced by a group A streptococcus of undetermined type, which the patient carried in his nose and throat for many weeks. Finally, this type disappeared, and eventually type 19 streptococci again appeared and were present in small numbers until the twentieth week. The signs of scarlet fever disappeared about the tenth day; and there was a quiescent period (phase II) for about two weeks, followed by a typical attack of rheumatic fever in which most of the clinical symptoms and signs of the disease were present. The electrocardiogram revealed partial heart block; and a few days later an apical systolic murmur appeared which persisted. This indicated the presence of mitral valvulitis. As the patient did not tolerate salicylates well, his antirheumatic therapy consisted of aminopyrine (pyramidon) which controlled the symptoms; but the laboratory evidence of persisting infection was of several months duration.

CASE II. This patient had a similar but less severe attack of scarlet fever due to type 19 streptococci. In this case the first course of sulfadiazine did not clear up the carrier state with respect to streptococci. A second course given from the thirty-seventh to the forty-

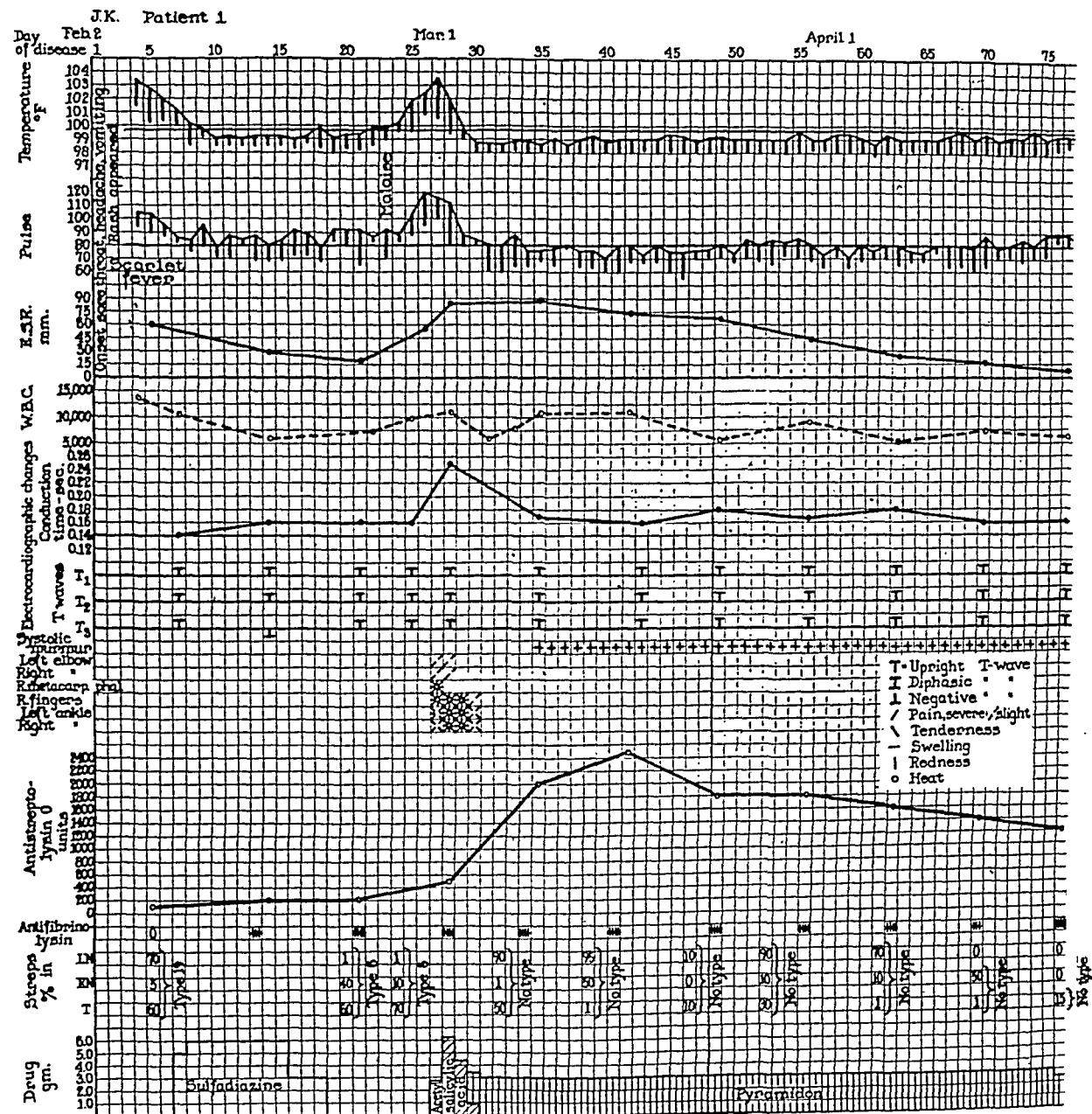


FIG. 1. Streptococcal infection (scarlet fever) followed by a two weeks' quiescent phase, then a typical attack of rheumatic fever with both polyarthritides and carditis.\*

second day, however, caused permanent disappearance of these microorganisms from the nose and throat. After a quiescent period (phase II) of over four weeks, there was evidence of active carditis as indicated by dropped beats, markedly prolonged conduction time, and the appearance of a mitral systolic murmur which persisted thereafter. Noteworthy was the absence of fever and the very slight evidence of arthritis, which consisted merely of pain in the

spine for three days. A reversion of the ESR from normal during phase II to 15 mm., and of leukocytosis was additional evidence indicating a rheumatic attack.

CASE III. In this patient the scarlet fever was more marked and prolonged than in the previous patient. Type 19 streptococci were evidently the offending microorganisms. These persisted for over eight weeks in large numbers in the nose and throat except for a period when the patient was under the influence of sulfadiazine. Here again, after a quiescent period

\* These studies were carried out in collaboration with Dr. R. F. Watson and Dr. Sidney Rothbard.

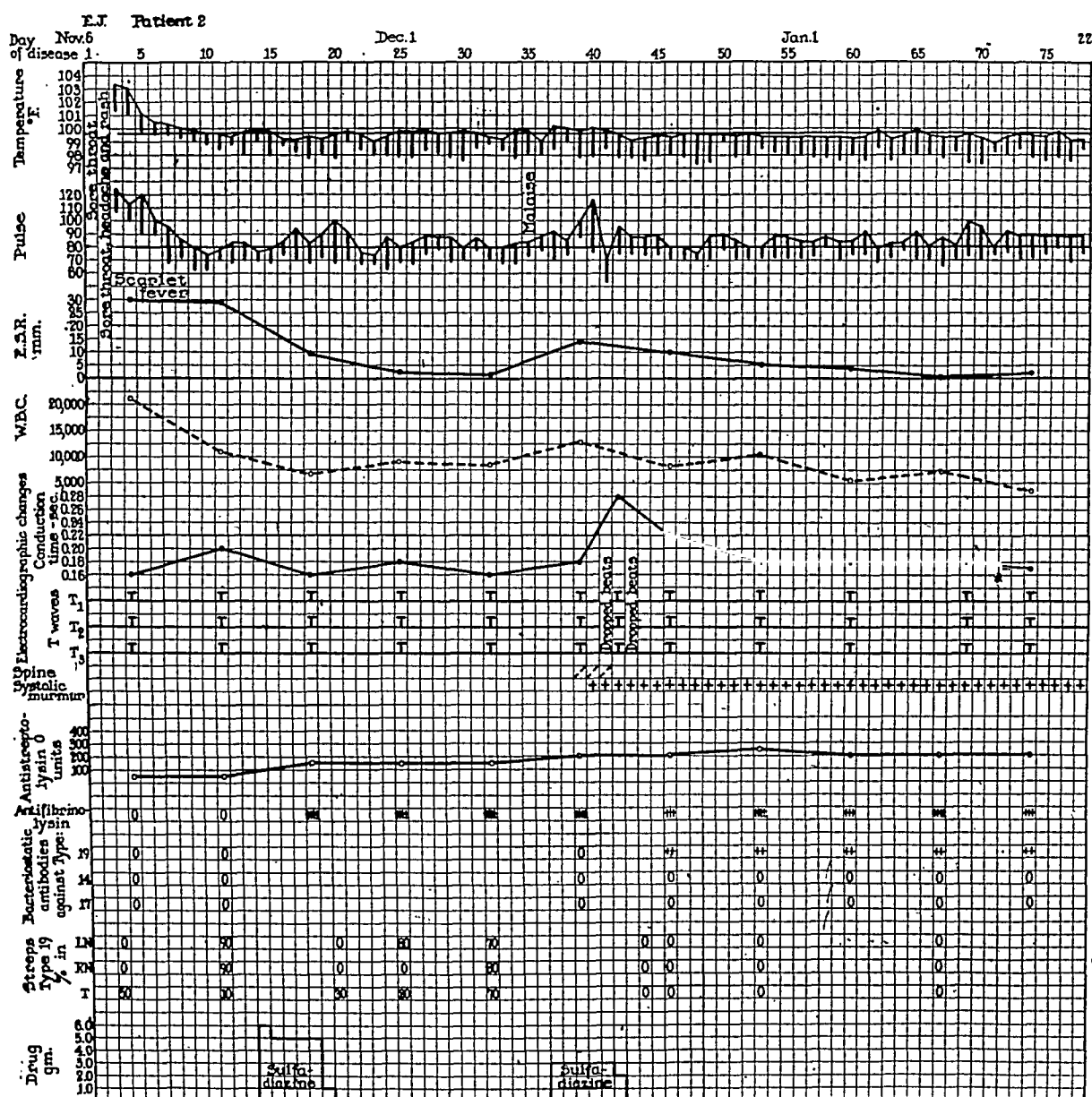


FIG. 2. Streptococcal infection, followed by a four weeks' quiescent period, then definite carditis, but no fever and minimal arthritis.

(phase II) of four weeks, there was evidence of a rheumatic-like attack, which consisted of a recurring abnormal ESR, leukocytosis, and a prolonged conduction time in the EKG. Obvious signs of rheumatic fever were conspicuous for their absence; hence one must hold in abeyance the certain diagnosis of this disease.

CASE IV. In this fourth case, the findings indicated a possible, but very questionable, rheumatic attack occurring much earlier, and consisting of pain in both elbows and slight precordial distress lasting four days. This was followed shortly by abnormal electrocardio-

graphic evidence such as diphasic  $T_1$ , then during the third week negative  $T_1$  and  $T_2$ , which disappeared gradually by passing through a diphasic stage. Later  $T_3$  became negative for about three weeks. The only other evidence of possible rheumatic fever was a temporary recurrence of abnormal ESR at the beginning of the sixth week. In contrast to the first three cases, it is to be noted that the evidence of cardiac and arthritic involvement occurred early during what would normally be designated as phase I. It is very questionable, therefore, whether these should be designated as truly

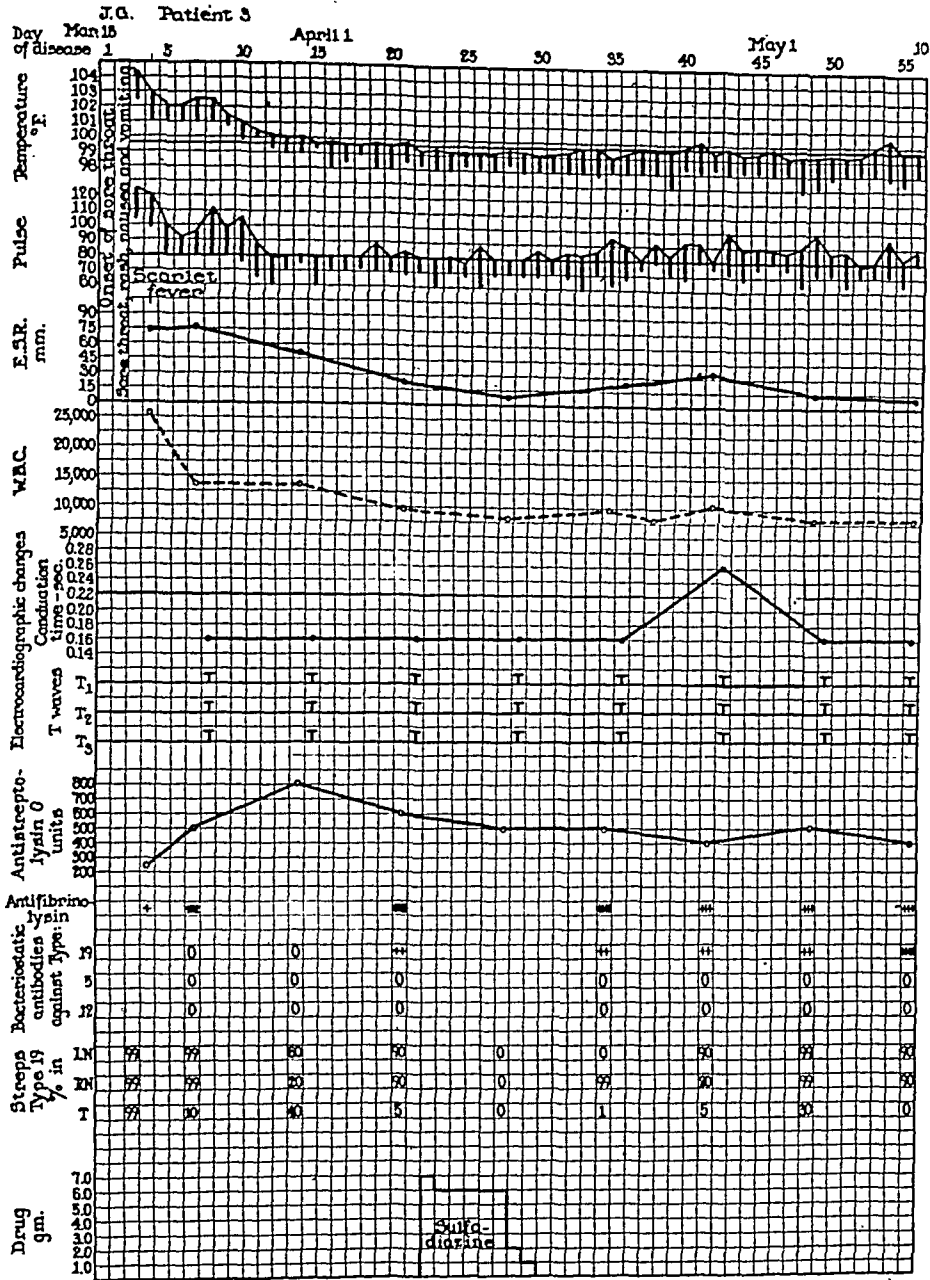


FIG. 3. Streptococcal infection, four weeks' quiescent period, then temporary indication of carditis.

rheumatic, because many patients have pains in the joints during the acute streptococcal episode; and electrocardiographic abnormalities similar to those shown by this patient are not infrequent in many febrile conditions.

It is to be noted in this case that the administration of sulfadiazine was followed by a permanent disappearance of streptococci from the nose and throat. This, in our experience, is an exceptional occurrence, and it must not be forgotten that a certain portion of patients with streptococcal nasopharyngitis show similar dis-

appearance of the microorganisms from their respiratory passages without the assistance of antibiotics.

The time of appearance and the intensity of streptococcal antibodies such as antistreptolysin O, antifibrinolysin, and bacteriostatic antibodies in the various patients are indicated on the charts. In all there was a fairly rapid appearance of antifibrinolysin. In all the antistreptolysin O titre became distinctly abnormal; but there seems to be no

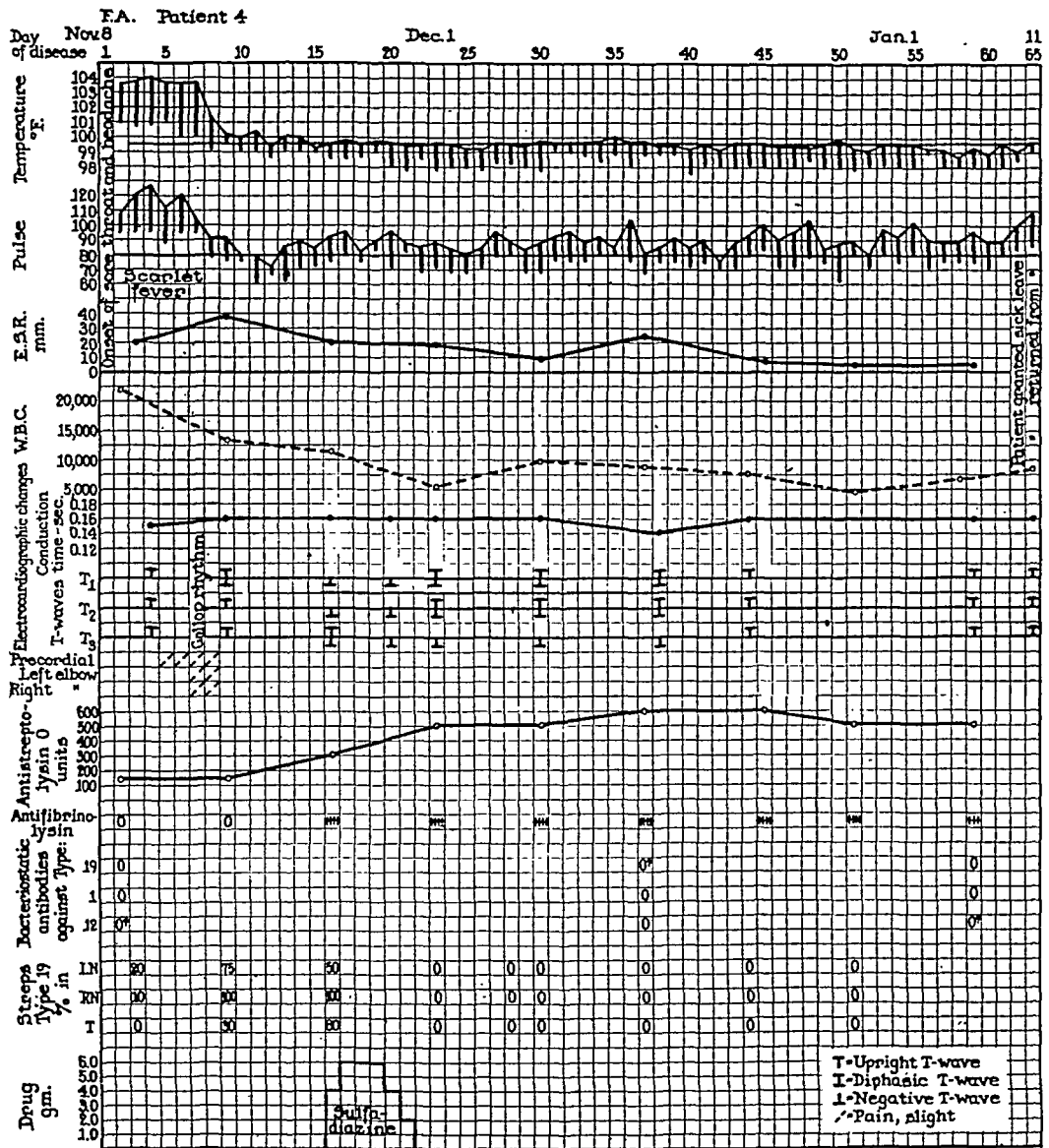


FIG. 4. Severe streptococcal infection accompanied by arthralgia and followed immediately by electrocardiographic signs of cardiac involvement.

general rule as to when this may occur. In two, no definite bacteriostatic antibodies were demonstrated; while in the other two, they appeared in moderate concentrations fairly early, but were not present in high concentrations until very late.

These four cases bring up the question of the difficulties in making a diagnosis of rheumatic fever. In Case I the clinical picture during the acute febrile episodes, phases I and III, were so typical of their respective states, and the development of a mitral systolic murmur subsequent to the

migratory polyarthritides was so characteristic, that the diagnosis was easily made without resort to any laboratory aids. In Case II the difficulties increase. There was an initiatory streptococcal infection, viz., scarlet fever; and during a relatively long phase II, all symptoms and clinical and laboratory signs of infection disappeared, except that type 19 streptococci persisted in the nasopharynx. Such a patient would ordinarily have passed from observation, for he probably would have disregarded the malaise on the thirty-fifth day. He remained

afebrile; and the slight pain in the spine from the thirty-ninth to the forty-first days might easily have been overlooked. The dropped pulse beats might have been considered as due to extra systoles, but their true nature was revealed in the electrocardiograms which showed a partial heart block, a fairly frequent occurrence in active rheumatic carditis. The concurrent appearance of a mitral systolic murmur which persisted thereafter was fairly conclusive evidence of valvulitis. Recurring abnormal ESR and distinct leukocytosis all fit into the pattern of an acute rheumatic episode. In fact, except for the differences in fever, severe intoxication and migratory polyarthritis during phase III, cases 1 and 2 are not dissimilar.

Case III, on the other hand, presented increasing diagnostic difficulties for during phase III there were only slightly increased heart rate, slight leukocytosis and moderately elevated ESR, but a distinctly, though temporarily, elevated conduction time, as revealed in the EKG. There was no stethoscopic evidence of carditis while he was under observation. According to current diagnostic criteria, it would be difficult to have the diagnosis of rheumatic fever accepted. How then is he to be regarded? Probably if he contracts subsequent group A streptococcal infections, his liability to develop a definite rheumatic attack will not be that of normal persons, i.e., about 10 per cent, but that of previously rheumatic patients, i.e., from 25 to 50 per cent.

Among 110 young adults with scarlet fever observed in The Rockefeller Institute Hospital,<sup>34</sup> seven showed during phase III evidence of a possible but questionable low-grade rheumatic episode, similar to that illustrated in Case III; four resembled Case II, but three showed no evidence of valvulitis; and eight had distinct rheumatic fever.

Many similar reports,<sup>30</sup> and also comparable findings following streptococcal naso-

pharyngitis,<sup>35, 36, 37, 38</sup> suggest that in allowing most patients to escape from observation during the two months following their acute streptococcal infection, we are failing to detect many early cases of low-grade rheumatic fever. It should be more widely recognized that many patients have rheumatic fever with little or no polyarthritis. Probably the incidence of the disease has not decreased to the extent indicated in hospital reports. Pathologists still see many cases where exitus is attributable to rheumatic carditis or chronic cardiac valvular disease; and the cardiac clinics continue to have a case load of from 30 to 40 per cent of rheumatic cardiacs among their total enrollment.

Additional evidence of the common occurrence of arthritis-free rheumatic fever occurs in the findings of Levy and his co-workers.<sup>39</sup> Among approximately 5,000 draftees who were rejected from induction for some form of heart disease, about one-half had definite signs of chronic rheumatic valvular disease. Two-thirds of this group denied any history of rheumatic fever or chorea; in fact, rheumatic disease was diagnosed for the first time when they appeared for the draft. It is quite possible that these men, while not having had true rheumatic polyarthritis, had a syndrome comparable to that described above; namely, a streptococcal infection followed by mild rheumatic disease without typical manifestations.

Further evidence of the close relationship between rheumatic fever and group A streptococcal infections rests in the demonstration that prevention of such infections by small, long continued doses of the sulfonamides prevents recurrence of rheumatic fever in rheumatic subjects exposed to such infections, while control patients not receiving these drugs develop the usual proportion of rheumatic recurrences following streptococcal infections.<sup>40, 41, 42</sup> Similarly, in

large streptococcal epidemics in military installations, where the epidemics were controlled by sulfa prophylaxis, there was a corresponding diminution in new cases of rheumatic fever.<sup>43,44</sup> A valid objection might be advanced: The sulfonamides might have had a prophylactic effect on the development of an unrecognized hypothetical "rheumatic fever virus." When, however, sulfa-resistant strains of streptococci appeared, and hence the epidemics were no longer amenable to sulfa prophylaxis, rheumatic fever occurred the same as among untreated controls.

It is furthermore noteworthy that neither the sulfonamides nor penicillin therapy have any beneficial influence on the manifestations of rheumatic fever, once they have appeared. Even the administration of large doses of these drugs during phase II, that is after the precursory streptococcal infection is established, apparently does not prevent the appearance of the rheumatic phase. These observations provide additional support to the probability that neither the sulfonamides nor penicillin has any effect on a hypothetical "rheumatic fever virus," and add weight to the conclusion that their beneficial influence upon rheumatic fever is in the prevention of the precursory streptococcal infection.

In weighing the evidence concerning the possible etiological role of streptococci in rheumatic fever, it should be emphasized that other infections have never been implicated as inducers of this disease. Respiratory diseases due to pneumococci, gram-negative bacteria, influenza viruses, or hypothetical viruses causing the common cold, have never been shown to set up a sequence such as is found between group A streptococcal infections and rheumatic fever. Furthermore, atypical pneumonia which frequently is accompanied by evidence of infection with the nonhemolytic streptococcus MG,<sup>45</sup> does not act as a precursor to

rheumatic fever. This points to the advisability of stopping loose talk about the connection between "respiratory infection" and rheumatic disease, and of emphasizing the unique sequential relationship between hemolytic streptococcal infections and rheumatic fever until the existence of this phenomenon is firmly established in the minds of physicians, public health workers and the laity. Once this peculiar relationship is understood, then it is comprehensible how rheumatic subjects can mingle with people having colds or influenza without the threat of rheumatic recurrences unless these diseases are complicated by group A hemolytic streptococcal infections.

If the highly probable and unique role of group A streptococcal infections in inducing rheumatic fever were generally accepted, then several important movements would logically eventuate. Instead of devoting the major portion of our efforts to the care of patients with chronic heart disease, much as these patients deserve attention, we would vigorously study more effective means of preventing the streptococcal infections whence flow the rheumatic fever sequelae. We would alter our attitude towards the apparently benign nature of scarlet fever, tonsillitis, and streptococcal pharyngitis because so rarely are they immediately fatal. During the years that usually lapse between the initiating streptococcal infection, the subsequent rheumatic attack, often asymptomatic, and the final picture of cardiac failure, so many events intervene, so many physicians attend the patient, that significant relationships often become obscured.

How group A streptococcal infections induce rheumatic fever has not been established. Much remains to be learned about the various chemical and enzymatic components which are present in the streptococcal cells or are liberated into their environment during their growth. More



must be known about host-parasite relationships with respect to these components. Our ignorance, however, should not become obstructive; it should not cause us to neglect the clearly established relationships so repeatedly mentioned in this communication and so often emphasized by many competent observers.<sup>46</sup> To quibble over the question of the etiology of rheumatic fever and to permit that quibbling to prevent applying effectively the partial, but very practical knowledge of this subject we now possess, is to serve our patients less satisfactorily than is within our power, and the public less effectively than it deserves.

#### DISCUSSION

DR. TARAN: Thank you Dr. Swift, for the scientific discourse on our present knowledge of the hemolytic streptococcus and the relationship of the streptococcal infections to rheumatic disease. This dissertation opens so many questions that we may easily drift off the subject of discussion. I suggest, therefore, that we try as far as possible to stick to the question of the hemolytic streptococcus and its relationship to rheumatic disease.

QUESTION 1: Has it been established that, when certain strains become resistant to the sulfonamides they belong to a specific type of hemolytic streptococcus?

DR. SWIFT: No. Sulfa-resistant strains have been discovered among several types, i.e., 1, 3, 6, 17, 19 and 30. These types have recently caused numerous epidemics in which the exposed populations have received mass sulfadiazine prophylaxis.

QUESTION 2: Is it good policy to let a scarlet fever patient out of bed after the symptoms have subsided?

DR. SWIFT: That depends upon the symptoms shown by the patient and upon both the clinical and laboratory signs of continued active infection. Rather than fol-

lowing a rule that covers all cases, it is probably more important to make erythrocyte sedimentation rate determinations every week or ten days for at least two months and to concentrate further observations on those patients with continuously high rates and on those in whom the ESR increases to abnormal heights after an intervening return to normal.

QUESTION 3: From the clinician's standpoint, are there any tests that one can do on a patient with scarlet fever which would justify us in letting the patient up?

DR. SWIFT: One is justified in allowing a scarlet fever patient up when the temperature and pulse are normal, there is no leukocytosis, and the ESR is fairly normal. This would probably be good practice with patients following streptococcal nasopharyngitis.

QUESTION 4: Am I justified in concluding from your remarks that if a patient is discovered to have a streptococcal infection, and is given adequate sulfonamide therapy or penicillin, that we might prevent an onset of rheumatic disease?

DR. SWIFT: You are not. This question has been covered in the body of this lecture.

QUESTION 5: Would you say that scarlet fever or another streptococcal infection is part of the rheumatic syndrome rather than that rheumatic disease is a result of the streptococcal infection?

DR. SWIFT: The first concept hardly seems logical because most streptococcal infections are not followed by rheumatic fever. On the other hand, most if not all cases of rheumatic fever are preceded by streptococcal infections; and it would, therefore, be more logical to say that the rheumatic syndrome is part of a phase of streptococcal infections.

QUESTION 6: Why should we not consider any type of streptococcal sore throat as belonging to the same category as scarlet fever, with respect to rheumatic fever?

DR. SWIFT: We probably should.

QUESTION 7: It has been said that rheumatic fever occurs commonly in families. Do you think that if we could give sulfanilamide to every member of the family where one case of rheumatic fever is known to exist we might prevent other members from coming down with rheumatic fever?

DR. SWIFT: If this prophylactic treatment were continued long enough and at proper times, it would probably be effectively prophylactic with respect to rheumatic fever with the provision that the patient was not exposed to sulfa-resistant streptococci.

QUESTION 8: How often does the streptococcus, which is found in the first phase, disappear in the second or third phase?

DR. SWIFT: Probably in approximately 25 to 35 per cent. This disappearance of streptococci in the interval between phase I and the onset of the rheumatic attack has been one of the stumbling blocks preventing certain observers from accepting the etiologic rôle of streptococcal infections in rheumatic fever. The argument is as follows: If the streptococci are the etiologic agents, they should be present and demonstrable at the time the active rheumatic manifestations occur. One should not lose sight of the fact, however, that this disappearance of the streptococci from the nose and throat does not prove that they are not still lurking and active in more inaccessible structures such as the paranasal sinuses or the lymph nodes draining these areas.

QUESTION 9: Is it true that the organisms that were present in phase one increase once again in the third phase?

DR. SWIFT: This is not true as a rule; for example, as mentioned in the previous answer, in about a quarter to a third of the patients the streptococci disappear. Usually in the other two-thirds there is a tendency towards a decrease in the number of recoverable streptococci, although in some there is a constant discharge of large num-

bers. These are probably the most dangerous persons with respect to distributing streptococci among healthy people. Doubtless, one of the most important health measures that might be devised would be to change the carrier streptococcal state of these patients.

QUESTION 10: Is it true that the incidence of rheumatic disease is greater at certain times of the year than at others? Is it also true that certain localities have a low incidence? Do these seasons and these localities also have a low incidence of streptococcal infections?

DR. SWIFT: The incidence of rheumatic fever shows a seasonal curve analogous to that of group A streptococcal infections. Also, the incidence of rheumatic disease follows closely the geographic distribution of streptococcal infections. These relationships are not absolutely parallel for in the tropics certain areas seem to have a comparatively small number of streptococcal infections, with a still smaller proportion of rheumatic manifestations. It seems as though these climatic conditions might favor the lack of development of rheumatic fever.

QUESTION 11: Have any cases of rheumatic fever been described which did not have a streptococcal infection preceding the onset of rheumatic fever? Let us say, in two hundred cases of rheumatic fever, how many are not known to have had phase I and phase II?

DR. SWIFT: One cannot give an exact answer to this question because there are only two ways of determining the presence of phase I: (1) by clinical observation which may be misleading because streptococcal infections of very low grade may occur without setting up observable clinical respiratory infections; and (2) bacteriologically and immunologically. If we could study all of these cases bacteriologically and immunologically for the presence of antibodies against streptococcal components, practically all would be shown to have a

phase I prior to the attack of rheumatic fever.

QUESTION 12: In your studies, what percentage of patients could be prevented from having rheumatic fever by preventing streptococcal infections?

DR. SWIFT: We cannot answer this question from our work; but all studies on this subject indicate that the large majority of patients could be prevented from developing rheumatic recurrences if they receive continually small doses of the sulfonamides before the attacks of rheumatic fever; again with the provision that they were not infected with sulfa-resistant strains.

QUESTION 13: With our present knowledge of the relationship of the streptococcus to rheumatic disease, have we the right to say that this relationship is the beginning and the end of the story?

DR. SWIFT: No; as I have attempted to point out in the concluding part of this lecture.

QUESTION 14: Or have we simply the right to say that the streptococcus may be one of the factors?

DR. SWIFT: It is probably one of a number. It is the only one about which we have fairly definite information. There is of course another question, that of the soil in which the streptococcus acts; in other words, the precursory attuning of the human tissues which will determine the course of the streptococcal infection. Dr. May Wilson will probably present much evidence suggesting that hereditary factors may condition the tissues. Other possibilities are subject to experimental demonstrations which doubtless will be made before the final answers are available.

## APPENDIX

### TECHNIC OF GROUPING AND TYPING STREPTOCOCCI

The following description of the technic for grouping and typing streptococci in

capillary pipettes is taken largely from the original article by Swift, Wilson and Lancefield<sup>10</sup> but slightly modified in the light of subsequent experience, especially in the use of pointed capillary pipettes for group testing.<sup>47</sup>

*Apparatus.* Capillary pipettes for *typing* are made from stock capillary tubing\*  $1.0 \pm 0.2$  mm. in external diameter which is broken into 7.5 cm. lengths. The external surface is cleaned with soft paper tissue but the inner surface is not cleaned because chemical treatment interferes with capillary action. The pipettes are placed in suitable glass test tubes.

Capillary pipettes for *grouping* are made from tubing  $1.5 \pm 0.2$  mm. in external diameter. This is broken into 12 to 13 cm. lengths; the middle of each length is heated in a narrow flame (such as is made by a fish tail burner or the pilot of a Bunsen burner) and when melted, drawn to a very fine point by quickly pulling on the two ends of the tubing. Thus two conically pointed pipettes are formed with fine openings about the diameter of a hair. The outer surface of these pipettes is cleaned with paper tissue, and they are placed in test tubes containing at their bottoms absorbent cotton on which the conical points rest. If strong grouping sera are available, 1.5 mm. pipettes may be prepared in simple 7.5 cm. lengths like the 1.0 mm. tubing. The test tubes containing the pipettes are capped with *unsized* paper, then sterilized by dry heat or by autoclaving, followed by drying in an incubator.

*Serum Containers.* Containers for sera in current use consist of two parts. The first is

\* The capillary tubing is made by the Kimble Glass Company, Vineland, New Jersey, and can be obtained from laboratory supply houses. It is described by that company as No. 46485 capillary pipette tubing, made of neutraglas (N-51A glass), not individually gauged, and varies in outside diameter from 0.7 to 1.0 mm. with 0.2 mm. wall. There are approximately 500 thirty-four inch lengths to the pound. For group classification, larger tubes with outside diameter of 1.2 to 1.5 mm. are used; 1 pound contains approximately 300 thirty-four inch lengths.

a small screw cap vial 45 mm. long and 15 mm. in diameter, with a neck having an inside diameter of 9 mm. The second is an inner container made of glass tubing with an external diameter of 7 to 8 mm. and an internal diameter of 5 mm. From this tubing a goblet-shaped cup is made, about 20 mm. deep, and standing on a solid stem and foot. The stem is cut so that the combined height of the stem and cup is 42 mm. The inner container which holds about 0.2 cc. is placed in the vial, and the cap attached. (Fig. 5.)\* Each vial, with the cap loosened, is wrapped in paper and sterilized in the autoclave. The vials are filled from the stock serum bottles with aseptic precautions. The sediment is allowed to collect in the bottom of the cups; and when loading the capillary pipettes care must be taken not to stir it up or to draw it into the pipettes.

*Vial Holder.* A wooden block holds two rows of vials, one behind and about an inch above the other. The holes to receive the vials should be  $\frac{5}{8}$  inch in diameter and  $\frac{3}{4}$  inch deep and  $\frac{1}{4}$  inch from margin to margin. A small piece of plasticine in the bottom holds the vials firmly so that they do not turn when the caps are unscrewed. (Fig. 6.)

*Capillary Pipette Stand.* This consists of a wooden block 10 in. long,  $1\frac{1}{4}$  inches wide and  $\frac{7}{8}$  of an inch deep. A groove  $\frac{1}{4}$  inch wide and deep is cut lengthwise on one side, and is filled with plasticine. Labels are written on narrow strips of ruled paper and fastened in front of the groove. One stand is used for each extract when the complete set of sera is employed. (Fig. 7.)

*Reading Equipment.* A dull black screen is placed beneath and a few inches behind an electric light so that the tubes may be observed with back-lighting against a black background. A fluorescent lamp is superior

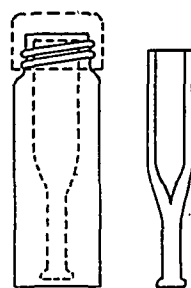


FIG. 5. Serum container in screw cap vial; detail to show shape.

to an ordinary incandescent bulb. The tubes are examined with a hand lens of about 5 diameters magnification.

#### Reagents.

- (1) N/5 HCl
- (2) Buffered N/5 NaOH made as follows:  
 $\text{Na}_2\text{HPO}_4$  (anhydrous salt) ..... 5.786 Gm.  
 $\text{KH}_2\text{PO}_4$  (anhydrous salt) ..... 3.532 Gm.  
 dissolved in N/5 NaOH. .... 1000.00 cc.
- (3) N/20 NaOH
- (4) N/20 HCl
- (5) 0.1 per cent solution of thymol blue
- (6) 0.1 per cent solution of phenol red

All solutions should be kept in pyrex containers, and any solutions containing precipitates should be discarded. Extracts prepared with buffered NaOH, when mixed with the precipitating sera, must not produce a degree of cloudiness that would interfere with the readings. If this occurs repeatedly, a simple N/5 NaOH solution may be substituted for the buffered alkali.

*Media.* *Todd-Hewitt Broth*<sup>48</sup> (*Modified*)—*Beef Meat Infusion Base:* Cut away as much fat as possible from fresh beef heart or horse meat. Chop or grind the lean meat fine and to each pound add 1,050 cc. of distilled water. Stir, and with a sieve skim off the small particles of fat which arise to the surface. Place the meat and water mixture in the ice box overnight. The next morning heat to 85°C. and maintain this

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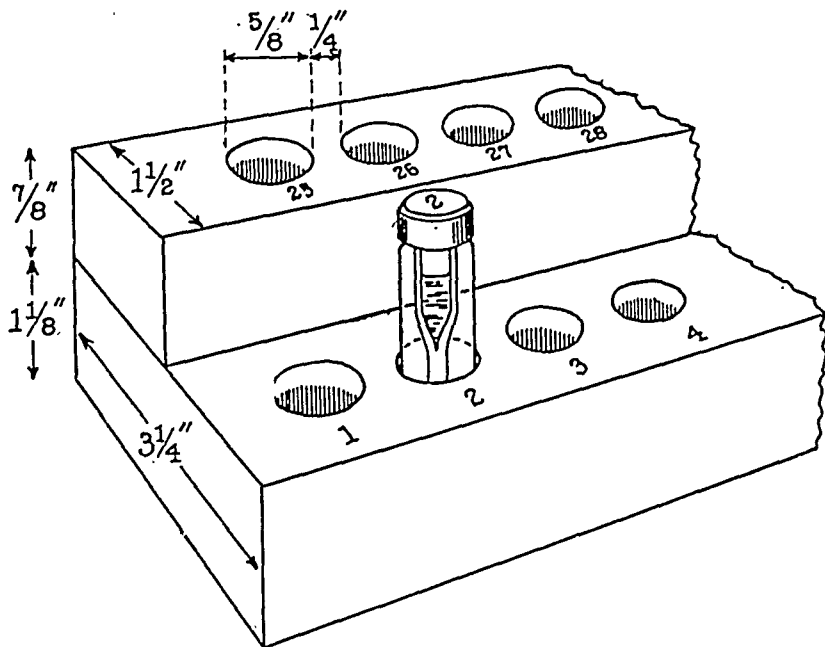


FIG. 6. Vial holder with one serum container in place.

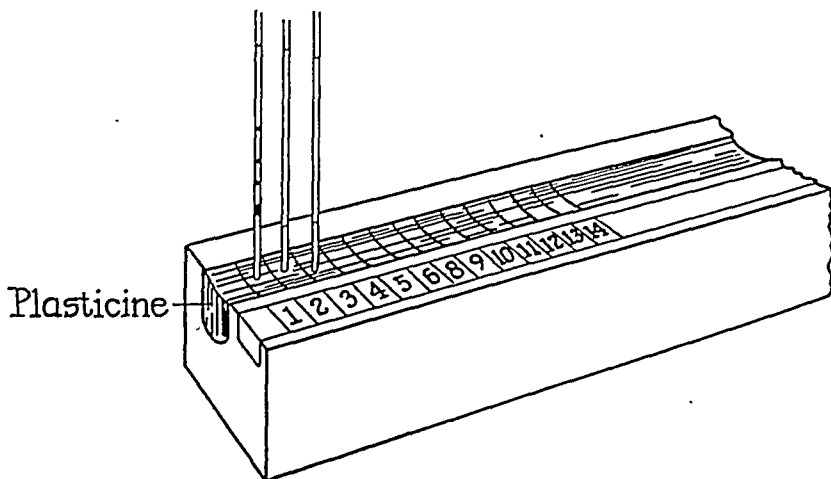


FIG. 7. Capillary pipette stand with three pipettes in place; precipitate in first tube indicates positive reaction with type 1 serum.

temperature for one-half hour. Filter the broth through coarse filter paper.

To each liter of the above infusion add 20.0 Gm. of neopeptone. Adjust pH to 8.0 with N/1 NaOH and add the following:

NaCl.....	2.0 Gm.
NaHCO <sub>3</sub> .....	2.0 Gm.
Na <sub>2</sub> HPO <sub>4</sub> , anhydrous.....	0.4 Gm.
Glucose.....	2.0 Gm.

Boil for fifteen minutes and filter through filter paper. Tube in 40 cc. amounts\* and sterilize in the Arnold for one hour on three

\*For facilitating later manipulation, it is convenient to tube the broth in 50 cc. centrifuge tubes.

successive days. The final pH should be 7.8. The fifteen minutes boiling should drive off the CO<sub>2</sub> prior to Arnolding. If not, a precipitate may be formed during sterilization. If this happens, the broth must be filtered and the pH readjusted under sterile conditions, followed by one hour in the Arnold. The anti-M proteinase<sup>49</sup> is inactive in this broth due to the use of neopeptone.

Blood broth for stock cultures may be prepared by adding two or three drops of defibrinated rabbit or sheep blood to 5 cc. of the Todd-Hewitt broth.

Good blood agar is needed for primary isolation of hemolytic streptococci from the throat and nose or from purulent material. It should be moist when inoculated and during incubation because dry media does not support growth well. Defibrinated rabbit or sheep blood is the most satisfactory blood. With the former, bacillus hemophilus hemolyticus shows hemolysis about the colonies, while with sheep blood this bacillus is inhibited.

*Preparation of Bacterial Extract.* Approximately 40 cc. quantities of Todd-Hewitt broth in 50 cc. centrifuge tubes are inoculated from the pure stock cultures and incubated at least eighteen hours or until a heavy growth is obtained. This is checked for purity of growth. The broth culture is centrifuged and the clear supernatant fluid is pipetted off or decanted.

The bacterial sediment is mixed with 0.4 cc. of N/5 HCl. A loopful of the suspension should give an orange red color with a drop of 0.01 per cent thymol blue, that is, the extractions should be carried out at a pH of 2.0 to 2.4. If necessary, more N/5 HCl is added to obtain this range.

The mixture is transferred to a pointed 15 cc. centrifuge tube and heated in a boiling water bath, shaken at three-minute intervals for ten minutes, cooled and centrifuged.

The clear supernatant fluid is decanted into a second centrifuge tube and a small drop of 0.01 per cent solution of phenol red is added, which colors the solution a distinct yellow.

0.3 to 0.33 cc. of double buffered N/5 NaOH is added drop by drop until a faint pink color appears. The first *faint pink* color is a pH of 7.0 and a good extract may have a pH between 7.0 and 7.8. If too alkaline, the extract is readjusted with N/20 HCl because non-specific precipitin reactions may occur when the pH of the extract is over 7.8. The slight precipitate formed dur-

ing neutralization is discarded after centrifugation and the supernatant fluid which should be crystal clear is pipetted or decanted into small test tubes. This is now ready for testing with antisera, and is used both for grouping and typing.

Difficulties in grouping and in typing tests are generally traceable to faulty preparation of the extract. It is essential that extraction be carried out at a pH below 2.5. It is also important to keep the final volume small. Cloudy extracts may be caused by contamination, by the use of N/5 NaOH stored in non-pyrex glass containers, and by stirring up of the sediment in the bottom of the centrifuge tubes. Contaminated extracts may give false reactions. All glassware must be perfectly clean; and the acid and alkali solutions must be of accurate normality.

*Preparation of Precipitating Sera.* Several different grouping and typing sera are commercially available. The typing sera are prepared by immunizing rabbits with heat-killed vaccines of streptococci known to be rich in M antigens.<sup>9</sup> After the serum is thoroughly absorbed with a strain of heterologous type to remove non-type-specific precipitins, it must react strongly with homologous M extracts in order to be useful in this reaction.<sup>12</sup> The absorbed sera, preserved with merthiolate 1:10,000, are conveniently stored in small dropping bottles from which about 0.2 cc. are transferred by means of the droppers to the small serum containers. Care is taken not to draw the precipitate which sometimes accumulates in the bottom of these containers into the capillary pipettes while performing the tests.

*Sterility.* Sera must be handled aseptically and kept sterile at all times. Except when in actual use, they must be kept in the refrigerator. Contamination is a frequent cause of cloudy sera, and of both false-positive and negative tests.

*Cloudiness.* All sera, particularly when freshly prepared, develop a fine precipitate which settles to the bottom of the container. This does not indicate deterioration, and may be allowed to collect unless it makes the sera cloudy. Some sera retain slight opalescence; and the technician must be familiar with these in order to avoid confusion or false-positive tests. Cloudy sera may be cleared by centrifugation or filtration through small Seitz filters.

#### CAPILLARY PIPETTE GROUPING

Grouping may be performed either for final identification, or as a necessary step in sorting out members of group A. In the latter case, it is necessary only to differentiate group A streptococci from the other groups.

The capillary group A screening test is usually run with a number of extracts just before the performance of typings. The bacterial extract, serum vials, capillary pipette stands, 1.5 mm. conical pointed capillary pipettes, and the equipment for reading are arranged conveniently.

*Procedure.* The sterile pointed end of a 1.5 cm. capillary pipette is dipped into the proper grouping serum until a column of serum between 1.0 and 1.5 cm. long has been slowly drawn in by capillary action. This end of the pipette is then wiped with paper tissue and dipped into a drop of extract until an equal amount of extract has been drawn into the pipette. Air bubbles must not separate serum and extract. The pipette is again wiped, then the conical end is plunged 1 or 2 mm. into a lump of plasticine in order to seal the hair-sized opening. The lower open end of the pipette is then pressed against a roll of plasticine which has been previously placed on the strip of plasticine of a capillary pipette stand. Thus the pipette will be held in a vertical position without being plunged into the plasticine, and in this way the fluid in

the top of the pipette will not be forced out by hydraulic pressure. The conical end of the capillary pipette should be inspected to see whether any extract has been forced out during this manoeuvre, and if this occurs, the minute drop should be wiped off so that no film is deposited on the pipette.

If the procedure has been properly followed, the column of fluid will be at the upper part of the pipette, and the sealing of the hair-like opening will insure that it remains there. The surface of the portion of the pipette containing the fluid should not have been touched by the fingers, hence should be perfectly clean. The lower air-containing portion probably will be finger marked.

The technic outlined insures the least possible amount of mixing of the underlying serum and the overlying extract; hence there is a narrow zone in which the precipitate forms. When longer columns of serum and extract are drawn into the capillary pipettes, this interzone moves over a wider range, more mixing of the two reagents occurs, and the zone of precipitate is wider; hence the reaction may be less intense. The same difficulty exists when the reaction is set up in 1.5 mm. pipettes with both ends open as previously recommended; rapid mixing of the two reagents occurs; and the reactions may be so indeterminate that they often require confirmation in small test tubes.

*Reading.* Within five to ten minutes a positive reaction is shown by a cloudy white ring of very fine precipitate at the junction of serum and extract. With weak sera or extracts, a longer time may be required. If the pipettes are placed in the incubator at 37°C. for an hour, weak cross reactions with sera of other groups may occasionally occur; hence readings made within five to ten minutes probably indicate more specifically the group to which the streptococci under examination belong. Upon standing the precipitate formed early may redissolve, or

it may clump, and fall to the bottom of the column of serum.

Errors due to weak reactions may result from excessive mixing of the extract and serum. Another source of error is to let the test stand too long before reading. False readings may result from grease marks or other materials on the outer surface of the tubes over the zone of reaction. Extracts and sera should always be crystal clear before preparing the test, since hazy sera or sediment drawn into the capillary pipettes with the reagents may lead to false-positive readings.

The pointed 1.5 mm. capillary pipettes are satisfactory for most grouping tests, but in some cases, larger quantities of serum and extract are required.<sup>9</sup> Place ordinary medicine droppers, with the bulbs removed, in a plasticine block so that the small ends are completely sealed. Place 0.05 cc. of the respective sera into each. Slowly pipette about 0.05 cc. of extract into each tube allowing it to layer over the serum. Within thirty minutes examine for a white ring of precipitate at the junction of the extract and serum. If the reactions are not clear cut, make extract dilutions of 1:4, 1:8 and 1:16, and test these dilutions. Similar dilutions may be tested in the larger pointed capillary pipettes. If cross reactions are still encountered, make a new extract by the formamide method and retest. The formamide method is only applicable to preparing extracts for grouping.

*Formamide Extract.*<sup>50</sup> Centrifuge 10 cc. to 15 cc. broth culture until the bacteria are packed; remove the supernatant as completely as possible and discard; to the sediment add 0.2 cc. of formamide. Shake; and place the tube in an oil bath (automobile or mineral oil) at 150°–180°C. for fifteen minutes; cool; and add 0.5 cc. of acid alcohol (1 cc. concentrated HCl with 99 cc. of 95 per cent alcohol); and centrifuge. Transfer the *supernatant* to a clean centrifuge tube;

add 1 cc. of acetone and centrifuge lightly; discard the supernatant. Add 2 cc. of normal saline to the *sediment*; shake, and add 1 drop of bromthymol blue indicator; then add sufficient 2 per cent sodium carbonate ( $\text{Na}_2\text{CO}_3\cdot\text{H}_2\text{O}$ , not "technical", sodium carbonate) to turn the extract blue. Centrifuge before use in the precipitin test.

#### CAPILLARY PIPETTE TYPING

In the presence of an epidemic due to hemolytic streptococci, both time and material may be saved by testing with the type serum covering the epidemic strain and with three to six other type sera as controls. Only if these give negative results need all of the sera be employed. Similar economies may be effected in testing repeated cultures from the same patient. These tests should be preceded by tests with group A serum.

*Procedure.* A container of capillary pipettes is mounted horizontally in plasticine; and capillary pipette stands, reading equipment, extracts and sera are arranged conveniently. Only those extracts are tested which have reacted with group A serum. The sterile end of a capillary pipette is placed in the serum until a column 1.5 to 2.0 cm. long has been drawn in by capillary action. It is next dipped into the extract, and an equal column is run in after the serum. If an air bubble separates the serum and extract, the pipette is discarded and another one set up. The column is allowed to run to the middle of the pipette, and the pipette is carefully wiped with soft paper tissue. It is then inserted into the plasticine of the pipette stand so that the serum is on the top of the extract. Similar preparations are made with each serum to be tested. (Fig. 7.)

*Reading.* As soon as a test has been set up, the tubes are examined for cloudiness with a hand lens and if foreign particles are present, the questionable pipettes are discarded and the test repeated. The pipettes



are incubated for two hours at 37°C. and preliminary reading is made. A final reading is made after the pipettes have stood overnight in the refrigerator. Most positive reactions will appear at the two-hour reading. When the extracts set up only against the common type sera give negative readings at this time, they may be set up immediately with the other sera. The following scale is used:  $\pm$ , just visible; +, a few fine masses visible with the hand lens; ++, usually beaded throughout, visible with the naked eye; +++, and +++++, column filled with larger masses of precipitate. Each positive test must be interpreted in the light of the known reaction of the serum with homologous extract. One plus or weaker readings should not be accepted as diagnostic.

True cross reactions are very rare. False-positives are usually caused by improperly prepared extract, or cloudy contaminated sera or extracts, or by dirty tubes. Whenever a particular test is doubtful, it should be set up again with serum, saline and serum, and homologous extract controls. Confirmatory tests may be performed by using larger pipettes or small test tubes, or with dilutions of extract. A strain should not be considered as untypable until several tests have been made by different techniques.

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# Heredity and Rheumatic Disease\*

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NEW YORK, NEW YORK

**A**LTHOUGH most clinicians are allergic to numbers, the statistical approach to rheumatic fever which has engaged our attention for several years has provided a framework within which various aspects of rheumatic fever may be explored.

In a lucid consideration of general principles of epidemiologic procedure, Frost states the following:

"In collecting facts about the distribution of disease, the purpose in view is always to a better understanding of its nature, sources, means of spread and eventually of its control. This implies that the facts must be related to each other in such an orderly way as to establish a theory or philosophy of the disease, given sufficient scope and accuracy of observation, a conclusion as to the nature and spread of a disease may often be established quite firmly by circumstantial evidence well in advance of experimental observation. Moreover, many problems of disease transmission which are highly important from the standpoint of prevention are such that can be solved only by investigation of this kind. The weakness in conclusions drawn from circumstantial studies is usually chargeable not to basic defects in the methods of investigation but more often to paucity or inaccuracy of data, or to faults of logic in their interpretation."

This approach has already yielded valuable information as to the nature of rheumatic fever, particularly as it affects attacked families in a clinic population in New York City.

*Genetic Risk.* It was demonstrated in genetic and epidemiologic studies that

hereditary factors were primarily responsible for the familial concentration of rheumatic fever. It was found that in these families the distribution of cases followed the general laws of recessive Mendelian inheritance.

Although at the present time the genetic susceptible child cannot be identified on the basis of recessive inheritance, the chance for each child in a family or group of families of known hereditary background to be susceptible can be expressed as follows: (Fig. 1.) If both parents are rheumatic, nearly every child will be susceptible. If one parent is rheumatic and the other parent is not rheumatic but a carrier, i.e., rheumatic fever is present among near relatives, each child has a 50 per cent chance to be susceptible. If neither parent is rheumatic but both parents are carriers, each child has a 25 per cent chance to be susceptible. If at least one child is rheumatic, it may be assumed that the parents are carriers. If one or both parents are non-rheumatic and non-carriers, susceptible children would be unlikely.

Genetic analysis of a series of rheumatic families revealed that the number of genetic susceptibles estimated in the families studied was found to be in close agreement with the final number of cases observed. (Fig. 2.) It may be postulated therefore, that distributed in the population, there are individuals who are susceptible or insusceptible to the development of rheumatic fever on a genetic basis. However, at the present time, it cannot be concluded that every genetically susceptible child will necessarily develop

\* Seminar conducted at St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, on October 23, 1945.

# GENETIC PREDICTION TABLE FOR CHILDHOOD RHEUMATISM

## EXPECTED PROPORTION OF RHEUMATIC CHILDREN

MATING PARENT		PRIOR TO OCCURRENCE OF A RHEUMATIC CHILD		SUBSEQUENT TO OCCURRENCE OF A RHEUMATIC CHILD	
1	2				
⊙	⊙		3%	■■■■	25%
⊙	⊙		3%	■■■■	25%
⊙	⊙		25%	■■■■	25%
●	⊙		3%	■■■■■	50%
●	⊙		16%	■■■■■	50%
●	⊙		33%	■■■■■	50%
●	⊙		50%	■■■■■	50%
●	●		100%	■■■■■■	100%

⊙ PARENT NEGATIVE, RHEUMATIC FEVER REMOTE OR ABSENT IN RELATIVES  
 ⊙ " " NO AUNTS/UNCLES AND FEW GREAT AUNTS/UNCLES RHEUMATIC  
 ⊙ " " FEW " " OR MANY " " " "  
 ⊙ " " ONE GRANDPARENT " " AUNTS UNCLES "  
 ● PARENT POSITIVE

FIG. 1.

## Comparison of Rheumatic Fever Cases Observed with Number Expected on Mendelian Recessive Assumption in Families with at least One Rheumatic Child

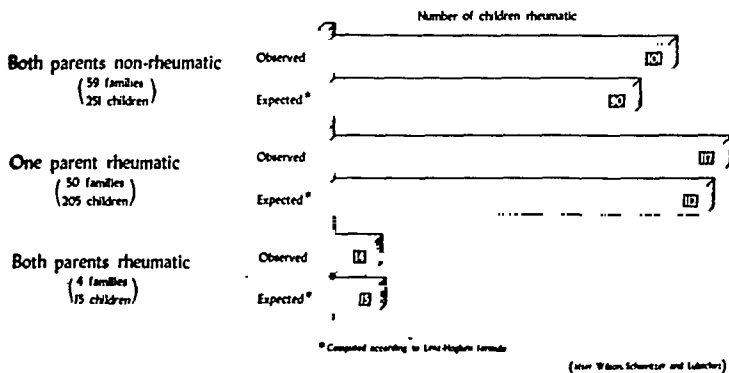


FIG. 2.

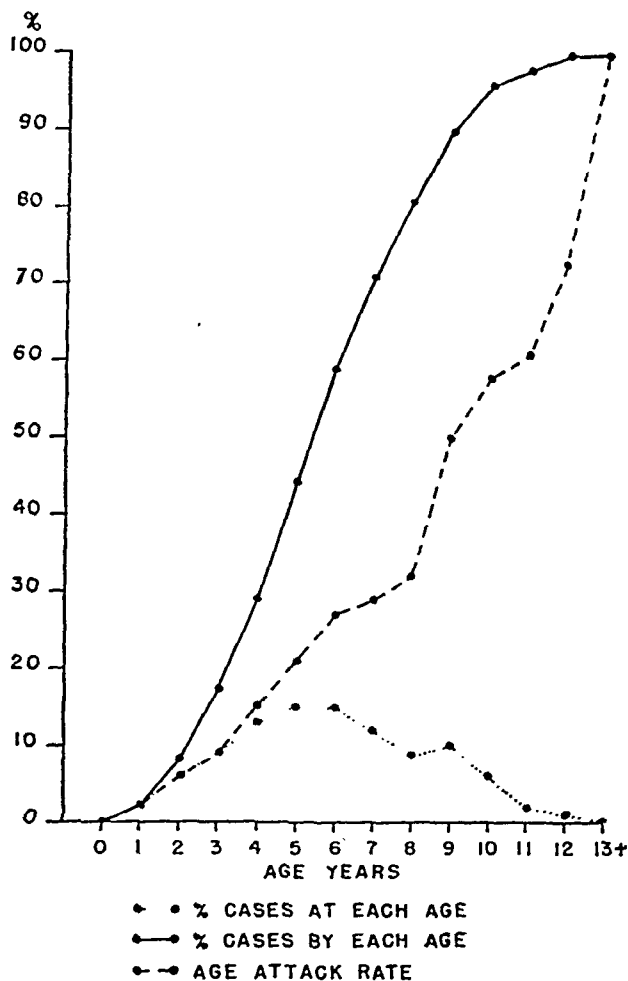


FIG. 3. Age factors derived from a rheumatic series of 688 cases of rheumatic fever at onsets.

rheumatic fever. It is probable that genetic analysis of a similar series of rheumatic families in comparable city populations would also show close agreement between the number of genetic susceptibles predicted and the number of cases observed. Whether the results of such genetic analysis made in Arizona or Louisiana or in a non-clinic population would be comparable must await the results of such investigations. It must be emphasized that the distribution of genetic susceptibles would not be expected to vary in various geographical localities and among diverse economic groups, although the frequency of rheumatic cases may. Should future studies of families reveal a difference in penetrance of the

disease, methods for the control of rheumatic fever would be available. There is urgent need for such studies to be undertaken.

It is clear that there are certain persons distributed in the population whose genetic make-up predisposes them toward having rheumatic fever. This genetic predisposition is a constant factor, from birth to death. Whether the disease will develop is probably dependent upon other factors, both within the individual organism and in the environment.

*Age Risk.* The age expression of rheumatic fever is probably one of the most important factors in the evolution of the disease. It has long been observed that rheumatic fever usually develops during childhood, from the age of four years to puberty, with an average age of onset of about six years. As Dr. Paul has aptly stated, "the infant must grow up to be rheumatic." In other words, there is an age factor in rheumatic fever which must be taken into account as well as the genetic background. For example, an infant, both of whose parents are rheumatic and who therefore has almost a 100 per cent chance to be rheumatic on a genetic basis, would not be expected to show symptoms of the disease until he had reached the age of at least four years or more. If this child is brought to the clinic at the age of two years, and the parents wish to know whether he will develop rheumatic fever during the coming year, it would be wrong to state that there is a strong likelihood, because at the age of two, few potentially rheumatic children have the disease.

In order to make a statistical evaluation of the age risk in rheumatic fever, the incidence of case onsets at various ages was calculated. These incidence rates represent the average chance a genetically susceptible child has for developing rheumatic fever at any particular age. (Fig. 3.)

AGE SPECIFIC RECURRENCE RATES FOR 499 RHEUMATIC INDIVIDUALS  
COMPRISING 5677 PERSON YEARS

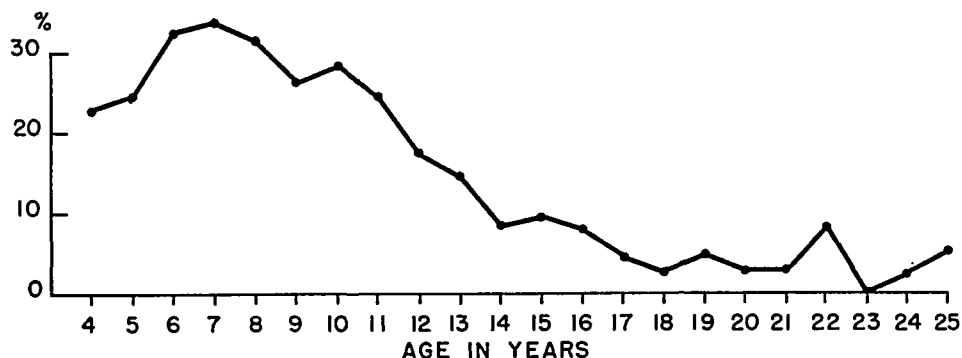


FIG. 4. Age specific recurrence rates for 499 rheumatic individuals comprising 5,677 person-years.

*Genetic-age Risk.* In 109 families studied, the genetic risk and the age risk were applied in combination, making it possible to predict the annual incidence of case onsets of primary and secondary cases, during the life experience of these families. That is, the intrafamilial pattern of spread of rheumatic fever was completely described by the use of age and genetic factors.

These observations are of epidemiological significance. They demonstrate that whatever factors are responsible for the onset of rheumatic fever among susceptibles, they were uniformly operative and effective during the entire life experience of these families. Furthermore, they demonstrate that rheumatic fever does not exhibit the usual characteristics of a communicable disease. It is unlikely that comparable observations could be obtained in any known infectious disease. On the other hand, similar findings might be demonstrable in a series of diabetic families. Should the genetic-age risk be found to be different in certain environmental situations, information about the rôle of specific environmental factors such as climate, diet and bacterial agents could be obtained.

It is not within the scope of this presentation to speculate as to the nature of the

inherent defect or to interpret the age expression of the disease. It may, however, be concluded that heredity is primarily responsible for the familial incidence of rheumatic fever and that the age risk determines the time of occurrence of cases in the family.

It is to be emphasized that statements about heredity in any disease refer to explicit cellular and functional attributes and properties whose precursors have a concrete and real existence in the genes. The hereditary character may be responsible for abnormal physiologic, chemical or hormonal reactions in the genetic susceptible host. Frequently a variety of exogenous factors may be necessary for the expression of the condition in the susceptible host without which the conditions will fail to be expressed altogether. It is therefore necessary to evaluate the effect of non-genetic factors such as environment, diet and bacterial agents, on the acquisition of the disease in a susceptible host.

*Risk of Recurrence.* Awareness of the importance of rheumatic fever has stimulated renewed efforts for its prevention. Current etiologic concepts form the basis for prophylactic therapy. In the present state of our knowledge of rheumatic fever, this approach is valid. If prophylactic therapy proves suc-

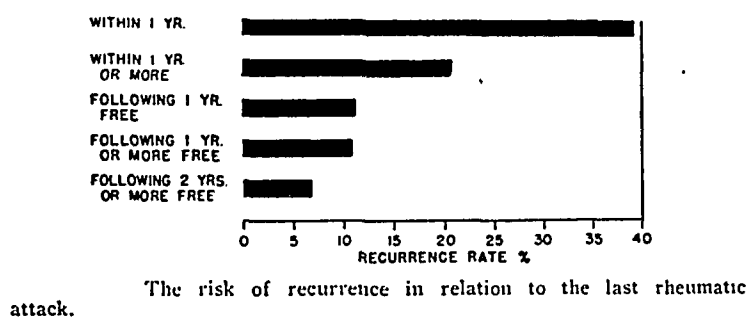


FIG. 5

cessful, in addition to the prevention of the disease, evidence for a basic etiologic concept would be obtained.

Here it is necessary to sound a note of warning if history is not to be repeated. It is necessary only to recall the premature reports of the prophylactic value of tonsillectomy.

The recently reported favorable results of sulfonamide prophylaxis have been widely accepted. Thomas, summing current published studies, observed that of 815 patient seasons over a period of seven years, incidence of recurrence was 1 per cent, compared with 10 to 35 per cent in untreated control groups. If these results are valid, the conclusion that all rheumatic children should receive therapy "day in and day out" would be justified.

However, critical analysis of published studies revealed that the individual studies did not meet the basic requirements for adequate biostatistical analysis. Selective and inadvertent bias characterized most studies. Rarely were alternate experimental and control patients selected. Frequently, patients were shifted back and forth from experimental to control groups. Such patients were usually uncooperative patients who refused treatment.

In many studies the experimental and control groups were not comparable because of differences in age constitution. In the majority of the studies, the groups were too small, and final conclusions were usually based on summated observations. This practice is only acceptable provided each

study which is included represents a random selection of patients. In addition, diagnostic criteria and observation must be uniform, environmental conditions and age constitution comparable. The published studies which have been summated in rheumatic fever do not appear to meet these requirements. It is obvious that final judgment as to the validity of the etiologic concept and consequent preventive therapy which are based on these studies must be deferred.

The clinical course of rheumatic fever is characterized by frequent recurrence of manifestations of the disease and a varying number of intercurrent years of apparent freedom from symptoms. Since current etiologic concepts and consequent preventive therapy are based in large measure on a comparison of the number of recurrences among experimental and control groups of rheumatic patients, it seemed important to define the average risk for a recurrence of rheumatic fever.

*Age-risk for Recurrence.* To obtain a measure of the expected risk of overt recurrence of rheumatic fever (arthritis, chorea, active carditis), a series of 500 records of patients representing 5,600 person years of life experience under continuous medical supervision were selected for analysis. It was found that the average over-all risk for a major recurrence was 25 per cent for patients between the ages of four to thirteen years, 9 per cent for patients between the ages of fourteen and sixteen, and about 4 per cent for those seventeen to twenty-five years of age. It is obvious that the risk of recur-

rences varies significantly with the age of the patient. (Fig. 4.)

Of particular importance was the observation that the risk of recurrence during the year immediately following a major episode was twice as great as that following at least one year of freedom and three times as great as that following at least two years of freedom from symptoms. (Fig. 5.)

Contrary to expectation, the rate of recurrence was not found to vary in twelve consecutive calendar years or with the number or severity of previous attacks.

The expected risk for a major manifest recurrence of rheumatic fever which has been defined should prove useful in evaluating the results of prophylactic therapy. It is to be emphasized for future studies to avoid selective bias alternate experimental and control cases should be included for study. To prevent inadvertent bias, the age distribution of experimental and control groups should be comparable and the period between attacks for the two groups uniform. Such bias in a small series might be responsible for any differences observed. The biostatistical studies which have been described have provided fundamental data on the nature of the risk for developing rheumatic fever, for onsets as well as recurrences. They indicate that the most important factor in the pathogenesis of rheumatic fever is susceptibility of the host. Future studies may reveal the nature of the factors responsible for the development of rheumatic fever among genetic susceptibles of a susceptible age.

It has become increasingly clear that the risk for the development of rheumatic fever resides primarily in the host. Here is a fruitful field for future research.

#### DISCUSSION

DR TARAN: The subject of heredity and rheumatic disease is now open for discussion. Are there any questions?

QUESTION: Is there any way of predicting how many members in a family will have rheumatic disease when both parents are known to stem from rheumatic families?

DR. WILSON: Yes. Numerical factors have been carefully worked out by geneticists for recessive inheritance in many abnormal conditions, i.e., albinism. It is a relatively simple analysis. For prediction, a tabulation of the number of families of one or more children according to parental status is made. Multiplying by the genetic factor on families of each size the number of susceptibles expected may be obtained.

QUESTION: The story is told, that a mathematician once set out to prove the law of probability by tossing dice to see what the chances were of getting seven or eleven. He found that the law of probability did not operate in this experiment. The number of sevens and elevens was significantly different from the mathematical prediction. However, to his great amazement, it was found that when the dice were weighed carefully, one of the dice weighed a fraction of a milligram more than the other. In other words, one of the dice was weighted only slightly, and it was this error that upset the mathematical law. Was inadvertent bias excluded in your studies?

DR. WILSON: Yes. Various tests indicated that there was no selective bias in the material analyzed.

QUESTION: Are there any factors in the individual or in his family history which makes him particularly susceptible to repeated attacks? Can we say that an individual that gets repeated attacks is one who has a higher degree of rheumatic disease in his family tree than the one who has only a single attack?

DR. WILSON: I do not know. We have obtained no evidence to indicate different degrees of inherited susceptibility.

QUESTION: Can we really say that the incidence of recurrences of rheumatic fever



declines with the age of the patient? Or do the manifestations in adult life evade diagnosis? We all are familiar with the fact that a patient may give a history of one acute rheumatic attack in childhood but will show consistent and progressive cardiac damage as years go by. Many of us have seen patients who have developed minimal cardiac damage in childhood and have apparently had no recurrent attacks throughout adult life, but at forty years of age are found to have markedly enlarged hearts with multiple valvular damage.

DR. WILSON: I do not think that is the complete story. While it is true that new murmurs will be heard that were not heard before, in the absence of recognizable recurrent rheumatic attacks, the findings may represent damage sustained during the original active process. This may take years to develop. We are all familiar with the fact that acute rheumatic fever is not limited to the childhood years and that many adults have acute attacks. But I believe we do not have sufficient evidence to say that so-called subacute rheumatic disease is present in all adult rheumatics who appear to develop progressive cardiac damage.

QUESTION: Isn't it true that rheumatic heart disease and rheumatic fever have been transmitted by injecting blood of rheumatics into normal individuals?

DR. WILSON: No. Rheumatic fever as such has never been transmitted. You are undoubtedly referring to the work that was done in England recently. What happened in that experiment was that blood from people who were suffering from an acute rheumatic attack was injected into normal individuals. Polyarthritis developed in the recipient. When the blood of this recipient was then reinjected into another group of normal individuals, a milder attack of polyarthritis resulted.

QUESTION: It is definite from your figures, that rheumatic fever is transmitted with a

certain gene. Can we say that in certain families a gene is labeled as rheumatic and that this will manifest itself in the progeny of this family as rheumatic fever?

DR. WILSON: Yes. That is the assumption for recessive inheritance. However, the disease is not transmitted, but only the susceptibility to the disease.

QUESTION: Have we a right to say that once a rheumatic child is discovered in a family, and the parents are known as being normal, that both of these parents must be genetic carriers?

DR. WILSON: Yes. That is the assumption on the postulate of recessive inheritance.

QUESTION: Have any studies been made to show why rheumatic fever has a low incidence among higher income groups? Is there any genetic explanation for the geographical distribution of rheumatic fever?

DR. WILSON: These questions cannot be answered at the present time, since we do not have factual data on either group. The second question could easily be answered by taking such groups of genetically susceptible individuals and transporting them to other climates to determine whether predictions would be realized. Genetic factors would not be expected to vary in different geographical areas, although the frequency of cases may.

QUESTION: Do you assume that if both parents have rheumatic disease, that all their progeny will have rheumatic disease?

DR. WILSON: One hundred per cent will be genetically susceptible to this disease and it is probably that one hundred per cent will develop it, at least in New York City.

QUESTION: Do you believe, on the basis of your observation that when susceptible children are transported to a subtropical climate before rheumatic disease has manifested itself, that the incidence will be the same?

DR. WILSON: I do not know. That remains

to be shown. Several such studies have been initiated.

QUESTION: How does this theory of genetics as related to rheumatic disease take into consideration the varied distribution of this disease in various locations in the same city?

DR. WILSON: I do not believe that we have any careful studies to support the premise of significant difference in distribution in various localities.

QUESTION: I believe that in a study in New Haven it was shown that rheumatic disease is distributed along the river front. How do you explain that?

DR. WILSON: River fronts usually have congested populations and many hospitals and clinics, which may well account for increased frequency of rheumatic fever in such areas.

QUESTION: In a previous session, we were shown that a milk-borne epidemic of hemolytic streptococcal upper respiratory infections was followed by an epidemic of rheumatic fever. How does this fit in with the genetic explanation?

DR. WILSON: We have to assume that in this group there were a great number of susceptibles. There are many epidemics of scarlet fever recorded without epidemics of rheumatic fever following them.

QUESTION: How can we explain a seasonal variation in the incidence of rheumatic disease on the basis of your concept?

DR. WILSON: As a matter of fact, a close analysis over many years shows that the incidence of rheumatic recurrences did not vary much from season to season. It is true that in the summer months in the City of New York the incidence of rheumatic disease is low. On the other hand, exceptions to the rule occur. This summer, for instance, we had a high incidence. It is a common experience that recurrences are apt to follow exposure and chilling. You take, for example, a child from one of the

inactive buildings here and let him go out into the rain and get his stockings wet, and he may get a recurrence.

QUESTION: Can we say that that same child would develop a recurrence without wet stockings?

DR. WILSON: He might.

QUESTION: If in your opinion the hemolytic streptococcus does not play an important role in the cause of rheumatic fever, then chemotherapy would not prevent rheumatic recurrences. May I ask you to give an explanation of the following occurrence?

The child came to the clinic several years with a history of chorea of five years' duration. Between the fifth and the sixth year, the child received chemotherapy in prophylactic doses. This year is the only year in which the child did not have any chorea.

DR. WILSON: You cannot be certain that chemotherapy prevented a recurrent attack of chorea. Chorea is a self-limited disease with varying years of freedom from recurrence.

QUESTION: Would you repeat the therapy?

DR. WILSON: No. I would not have given it in the first place. I know that we like to do something for the patient but we must keep our two feet on the ground. Until it can be definitely shown that prophylactic chemotherapy prevents recurrence, it is inadvisable to use a drug which may in some instances have deleterious effects. Some years back, the panacea for rheumatic recurrences was tonsillectomy. Every child had its tonsils removed. We soon found out that it made no difference in the incidence of rheumatic recurrences. This form of therapy was therefore given up.

QUESTION: Would you say that infection may be an added factor in the causation of rheumatic disease?

DR. WILSON: I do not know. But it is certainly worth while to find out. We now have a tool which we can use. The risk of rheu-

matic recurrences is worked out carefully and if we apply this risk to the study of the incidence of rheumatic recurrences in patients receiving prophylactic chemotherapy, we might get the evidence.

QUESTION: Rheumatic disease is, in the eyes of the clinicians, an illness which behaves very much like an infection. The clinician further feels that we now have certain drugs which are universal bacterial killers, such as penicillin, and sulfonamide derivatives. Would you not be willing to use these universal killers on the basis that the disease behaves clinically like an infection?

DR. WILSON: If the proper study were made, it would serve to end the doubts in this direction but no such study has yet been done to meet requirements for adequate statistical analysis. I believe that if these drugs are to be used, they are to be used experimentally only. In addition, we must be certain that these drugs do not have harmful effects. Certainly, as far as sulfon therapy is concerned, enough harmful effects have been observed to cause the army and navy to discontinue its routine prophylactic use.

It is admitted that the literature gives the general practitioner a feeling of confidence in the use of sulfon therapy as a prophylaxis of rheumatic disease. None of the evidence I have shown before indicates that sulfon prophylaxis prevented rheumatic recurrences. Until we know more about the factor or group of factors which may be responsible for the manifestations of rheumatic disease in a susceptible individual, we should limit prophylactic chemotherapy to experimental studies.

QUESTION: How do you explain racial difference in the incidence of rheumatic disease? We were told, for instance, that

rheumatic disease is less common among the colored people?

DR. WILSON: I do not believe that adequate studies have been published to support this observation. It depends on where you are studying these cases. In the hospitals where one racial or religious group predominates, there will be a greater incidence of rheumatic disease within that group.

QUESTION: Do you advise a positive by positive mating not to have children?

DR. WILSON: I would explain the risk to them carefully, and leave it to their judgment.

QUESTION: How about a positive by negative mating?

DR. WILSON: I would tell them that if the negative side of the family is free from rheumatic fever, the chances are small that any of the offspring will have rheumatic disease. If, however, close relatives of the negative parent are rheumatic, I once again would explain the risk and leave it to their judgment.

QUESTION: It has been said that children grow up to become rheumatic. In other words, rheumatic disease manifests itself not at birth, but several years after birth. Is there any explanation why in the same family, under the same environment, with the same rheumatic background, one child should manifest the disease at six years of age and the other one at thirteen years of age?

DR. WILSON: We cannot predict as yet which child in the family is going to get rheumatic disease and at what age, but we can definitely state what proportion in a given family with a given background, will develop rheumatic disease at each specific age. For the present, we have no explanation for the age incidence.

# Combined Staff Clinics

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## Lymphomas

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. JOSEPH C. TURNER: The central part of this morning's discussion on the lymphomas and recent advances in their therapy will be undertaken by representatives of the Department of Radiology and the Department of Pharmacology. But meanwhile, before introducing these investigators, I should like to recount briefly certain studies that have occupied workers interested in the field for some years, and to take note of what progress has been made.

The lymphomas, you will recall, constitute a group of tumors marked by prominent involvement of the spleen and lymph nodes. The term itself is merely a convenient one for the use of both clinician and pathologist, and should carry no connotation regarding the fundamental relations of these diseases to one another.

We include among the lymphomas the leukemias, Hodgkin's disease, the apparently true tumors of the lymph nodes—lymphosarcoma and reticulum-cell sarcoma—as well as the somewhat unusual, so-called giant follicular type, which runs a somewhat more benign course than the others, but in time, like them, becomes what is evidently malignant disease.

From the time that Sternberg first described accurately the characteristic pathology of Hodgkin's disease there have been persistent and patient efforts to remove this disorder from the neoplasms and to identify it as an infectious disease. There have been many reasons for this, notable among them the histological picture, for,

in contrast to the general run of tumors, Hodgkin's disease is marked not by the proliferation of a single type of cell but rather by the appearance of a pleomorphic growth. Included in the lesions are reticulum cells, as well as eosinophils and giant cells and there is usually considerable proliferation of fibrous tissue, too. Thus the histological features suggest some sort of infectious granuloma.

At first the belief was widely held that this might represent an unusual form of tuberculosis, because tuberculosis is found with unusual frequency in Hodgkin's disease. Some autopsy figures give an incidence of active tuberculosis as high as 20 per cent in classical Hodgkin's disease. This is perhaps twice what might be expected. But it appears that the tubercle bacillus is probably a secondary invader, assuming a heightened degree of virulence presumable because of some alteration in the resistancy of the host occurring in consequence of Hodgkin's disease. Numerous attempts have been made to recover tubercle bacilli from the lymph nodes and spleen of Hodgkin's disease but not more, I think, than perhaps 10 per cent of the cases show acid-fast bacilli either on section or by guinea pig inoculation.

From 1910 to 1920, there were reports of the cultivation of bacteria of various types, especially diphtheroids, from Hodgkin's disease. More recently, the claim has been made that *Brucella* organisms may be recovered with great regularity. It seems

unlikely that any of these infectious agents has etiological significance.

Between 1920 and 1930, an extensive program of bacteriological investigation was undertaken in England under the aegis of Dr. Mervyn Gordon and the findings were later published as "The Rose Research in Lymphadenoma." Gordon and his colleagues undertook to repeat all the bacteriological investigations of the past, looking for tubercle bacilli, spirochetes, fungi, etc. Their most notable contribution was the discovery that the lymph nodes in Hodgkin's disease contain a factor which is capable of producing encephalitis in rabbits. It now appeared for the first time that this disease might be transmitted to an experimental animal and could be caused by a virus. Unfortunately, however, further study of this agent of Gordon showed that it was not truly infectious since it could not be transmitted from one animal to another in series. Moreover, it was finally shown that the agent was not specific for Hodgkin's disease but was associated rather with the eosinophil, whether found in the lesions of Hodgkin's disease or in normal tissue. So that, although the past forty years and more have seen a number of attempts to identify Hodgkin's disease as a bacterial or a viral infection, none has succeeded and the question remains open.

The paramount difficulty, of course, has been the failure to reproduce the disease in an experimental animal. This consideration leads us to direct our attention briefly to what may fairly be said to be the most notable recent advance for the study of lymphoma, namely, the development of strains of animals with spontaneous leukemia.

The earliest systematic work on the subject was done by Ellermann about 1908, when he showed that the erythroleukosis of fowls could be transmitted from one animal to another, and furthermore, that he could

recover a filtrable agent which was capable of reproducing the disease. Since then this is recognized as a disease due to a filtrable virus and, as you know, there are several other bird tumors that represent viral infections.

In 1929, Richter and McDowell, by inbreeding, produced a leukemic strain of mice. There was now available in the field of mammalian lymphoma an experimental animal which could be subjected to controlled investigations. Since that time there has been a great deal of work done with mouse leukemia and there are now a number of strains which develop spontaneous lymphatic leukemia or lymphosarcoma, as well as myeloid types of leukemia. The animal disease resembles very closely the human one. Smears of bone marrow and peripheral blood, as well as sections of the various affected organs, look so much like the counterparts in the human that they are virtually indistinguishable.

Opportunity has been taken in the past decade to investigate the influences of genetic pattern, of mother's milk and of numerous other factors on the development of animal leukemia. It has been possible also to make certain biochemical observations, including the comparative metabolic behavior of tumor cells, the effects of hormones and therapeutic agents on the tumor, and so on. These advances emphasize once again the importance of the experimental animal in the special problem of cancer.

STUDENT: Have any biological tests for lymphoma been developed that can be applied clinically?

DR. TURNER: Unfortunately, no. The diagnosis still rests on biopsy of affected tissue, usually superficial lymph nodes. In this respect, the most important rule to be observed is: in any non-leukemic case of lymphoma, biopsy must be done before therapy is undertaken. Mistreatment of tuberculosis and other infectious granulomas,

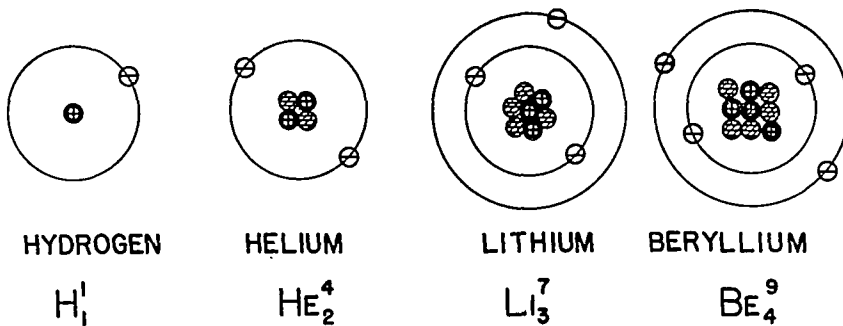
SIMPLE ATOMS

FIG. 1. Showing the "solar system" concept of the atom. Note the orbital electrons and the nucleus made up of protons (dark) and neutrons (light).

which may be indistinguishable from lymphoma clinically, is otherwise inevitable. Exceptions to this rule should be made only when biopsy is impracticable, as, for example, with a mediastinal lymphoma in a patient presenting no palpable superficial nodes in the neck or elsewhere.

We are fortunate this morning in having Dr. Quimby of the Department of Radiology to tell us something about radioactive isotopes, which have been introduced within the past ten years for the treatment of malignant disease. Perhaps their most notable success has come in the field of lymphoma.

DR. EDITH QUIMBY: Radioactive isotopes should not be considered by themselves in discussing the treatment of any disease, but rather they should be regarded simply as one source of radiation; therefore, the possibilities of the whole field of radiation therapy should be considered in any such discussion. What are the radiations which are available and usable? Where are they obtained and how are they controlled? How do they produce the effects which are observed?

In the treatment of the lymphomas the two types of radiation which are used are  $x$ -rays and the radiation from artificially radioactive substances. As to  $x$ -rays, your reaction to them is probably that they come out of  $x$ -ray tubes and are under the control

of the radiologist; he knows how they should be used and you will consult with him—and that is probably all right. As for the artificially radioactive substances, in a few years you may be just as blasé. You may believe that they come in a bottle with the specified dosage and you give them; but that, at the present time, is not the case. Because these are such new substances and because there are very few specialists in their use, it seems profitable to discuss their origin and nature briefly.

In order to do that, one must begin with atoms (since these are the elementary particles of matter from which the radiations come), and with the present day "solar system" concept of the structure of the atom. This concept of atoms (Fig. 1) supposes that each consists of a positively charged nucleus, which carries essentially all the weight of the atom, and a system of orbital electrons, each electron having a negative charge, with just enough electrons to balance the positive charge of the nucleus. This discussion is concerned only with nuclei.

Artificially radioactive substances are substances whose nuclei are in an unstable condition. Nuclei of atoms are built up of two kinds of particles, each having about the same mass: a particle which has no charge and which is called a *neutron*, and a particle

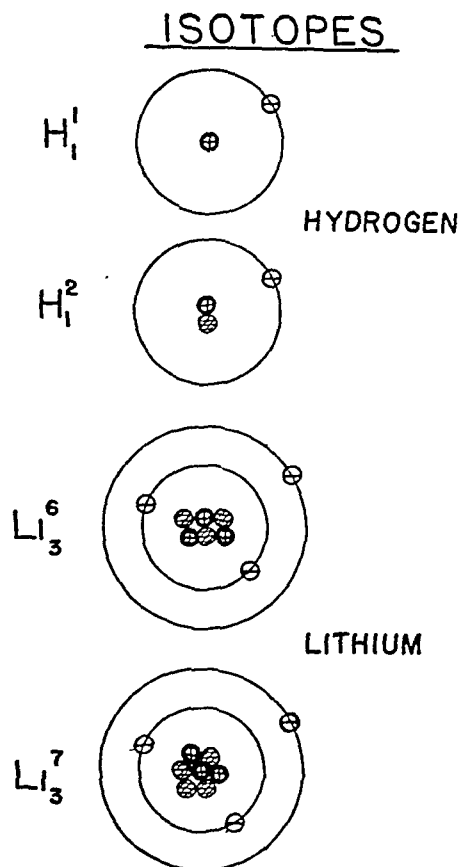


FIG. 2. Isotopes of hydrogen and lithium containing an extra neutron in each nucleus.

which has a unit positive charge and is called a *proton*.

In proceeding from element to element in the periodic system, the number of protons is increased by one. Hydrogen, the lightest element, has one proton in its nucleus, helium has two, lithium three, beryllium four, and so on. The number of protons in the nucleus is the *atomic number* of the substance; it is that which determines its chemical nature. For every number from 1 to 94 there is an element, and that element is defined by its atomic number.

The number of neutrons in the nucleus varies. It may be the same as the number of protons or greater to almost twice as many. The sum of neutron and proton numbers is the *atomic weight*. The symbols for the elements now are written not only with the customary chemical abbreviation

but with a subscript which gives atomic number and a superscript which indicates atomic weight, thus defining the element exactly.

As I said, the atomic number is fixed for each element but the atomic weight may be variable. Some elements have atoms of only one atomic weight and others have as many as seven or eight or even more different atomic weights for one atomic number. This is due to varying numbers of neutrons with the same number of protons.

Thus (Fig. 2) there are the two types of hydrogen: ordinary hydrogen, the nucleus of which is just a proton, and heavy hydrogen with a proton and a neutron. Atoms having the same atomic number and different atomic weights are called *isotopes*.

The lighter atoms have simple nuclei. In ascending the atomic scale, nuclei contain more neutrons and more protons and become more and more complicated. They are not rigid assemblages of particles. There are within the nuclei forces and activities going on which render these complicated nuclei unstable. Such nuclear instability means that at some time a nucleus will no longer be able to maintain itself the way it was but will react by ejecting a small part of itself. This phenomenon we call *radioactivity*. All elements with atomic numbers above 83 are naturally radioactive, that is, at some time during their existence such radioactive atoms become unstable, expel a small portion of themselves, (which may be, in the case of the naturally radioactive substances, a group of two neutrons and two protons) and settle down as atoms of different elements.

Artificial radioactivity is the making of atoms which are normally stable, unstable in the same way as naturally radioactive atoms exist in the state of nature. This can be accomplished by shooting into such a stable nucleus an extra particle, thereby putting it in a strained state. That extra

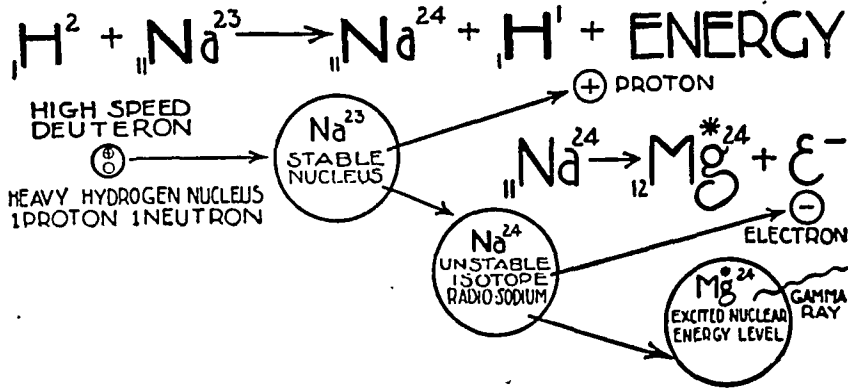


FIG. 3. Indicating the production of artificial radioactive sodium by bombarding normal sodium with the nuclei of heavy hydrogen.

particle may be a neutron or a proton, a deuteron (the nucleus of heavy hydrogen), an alpha particle from naturally radioactive material or possibly some other small agglomeration of nuclear particles. What happens then is that the new nucleus, the one with the extra material in it, is unstable and disintegrates in the same manner as naturally radioactive substances do.

One characteristic which it is important to remember about radioactive substances is that, although the disintegration of any particular atom is a completely haphazard affair, statistically, for any particular radioactive substance, half of all the atoms present will have disintegrated during a certain period; during a subsequent equal period half of what is left will disintegrate, and in another period half of that, ad infinitum. Therefore, by means of a simple mathematical expression, one can always calculate how much material should be left if it is known what was started with, or one can always calculate what should have been present in the beginning if it is known what is present at any particular time.\* These half-lives, as they are called, vary for different substances over an enormous range,

from fractions of a second to millions of years. For the artificially radioactive substances which have become useful in experimental or therapeutic work, the half-lives are of the order of days or weeks, or in a few cases, of a few months or years.

Figure 3 represents a typical example of the sort of thing that happens. This is the manufacture and disintegration of radioactive sodium. Ordinary stable sodium is bombarded in a cyclotron with the nuclei of heavy hydrogen, deuterons. The deuteron goes into the sodium nucleus, apparently breaks apart and the proton comes out. The neutron stays in, therefore making an unstable sodium having an atomic weight of 24, one more than normal sodium. This cannot exist the way it is, so one of the neutrons inside breaks down into a proton and an electron. The electron is expelled. That means that the substance now has 24 positive charges instead of 23. It is not sodium any more but is magnesium. In settling down to its normal state, the magnesium expels a gamma ray. Thus radioactive sodium gives out a beta ray (an electron), and a gamma ray in the course of its disintegration. So for the purposes of therapy there are available in addition to the x-rays, the beta and gamma radiations from certain radioactive substances.

How can these substances produce reactions in the living tissues? What is the phe-

\* The equation is:  $Q = Q_0 e^{-kt}$  where  
 $Q$  is the amount at future time  $t$  days hence  
 $Q_0$  is the amount of substance at present time  
 $e$  is the base of natural logarithms  
 $k$  is the decay constant per day and may be obtained  
 from the relation  $50 = 100 e^{-(k \times \text{half period})}$



nomenon by which energy is transferred from the radiation to the matter? The only way that anything can be done, as far as is known, in this universe is by the use of energy or the transfer of energy from the doer to the recipient. The way energy is transferred from radiation to matter is by a process called *ionization*. This is not the sort of ionization which occurs in chemistry—the breaking apart of molecules into positive and negative ions. This is the removal of an electron from the atom, leaving the atom in a charged state. If an electron is taken out of an atom there is left an atom with too few electrons to balance the nucleus. That is a positive ion. The electron itself or anything to which it may attach itself is the negative ion. The state of ionization lasts very briefly, but during that state abnormal or unusual atomic groupings may occur. For instance, if the atom were a part of a molecule and the electron pulled out was one of the binding electrons, the whole molecule might well break down. It is during the process of ionization that the changes come about which set in motion the ultimate biological change. From there on very little is known about what happens. That is one of the fields in radiobiology which must be investigated a great deal more.

The sort of track which the ionizing particle makes depends largely on its speed and energy. There may be a lot of ions crowded close together in a short path, or they may be spread out along a longer track, depending upon the speed of the particle, the energy of the x-ray or the speed of the beta ray which does the ionizing. If there is intense ionization, crowded together in one or two cells, a different result may be expected from that where the same number of ions that spread out over a great many cells. What steps occur after ionization to bring about biological changes is not known.

What are the final results in the cell? They are things which can actually be observed:

increased acidity of protoplasm, increased permeability of membranes, clumping of nuclei, breaking of chromosomes, halting of cell division, and finally, entire stoppage of all cell activity.

A little radiation may not produce any visible effect or it may produce some effect in some cells. A little more produces more effect, just like any other kind of drug, until finally an irreversible change results. If all living cells responded in the same way to radiation, it might be impossible to bring about any action upon specific cells. However, even in cells that are all alike some respond more readily than others. In cells that are different there are groups of cells which are much more radiosensitive than others. Fortunately, the lymphoid cells are the most radiosensitive of all. Following them are the epithelial and endothelial cells, and then connective tissue, bone, fat and nerve, in that order. Therefore, if radiation is poured into a mixed kind of tissue, a greater reaction may be expected in lymphoid tissue than in any other, and that of course is desirable in the treatment of disease of lymphoid cells.

In the diseases with which we are concerned, one may want to treat just a local growth, either lymph nodes, enlarged spleen, or something of that sort, or one may want to give a generalized irradiation. When the treatment is to be by means of x-rays, the treatment is adapted to each patient. It may be administered over the diseased areas, over blood-forming areas, or over the whole body, depending upon the radiologist's idea in the beginning and the patient's response as therapy goes on. If a great deal of the body is involved, not nearly as much radiation to any particular region can be tolerated. In this connection, the measurement of x-rays becomes important.

The unit of x-ray dosage is the *roentgen* and it is a queer kind of a unit. It is in essence the amount of radiation which produces a

certain number of ions in every gram of tissue on which this beam of radiation falls. A skin dose of 100 roentgens means that every cu. cm. of skin, and immediately underlying tissue, will be ionized to that extent; the tissues lying below the skin will be less ionized because some radiation will be absorbed. If a very small field in the skin is irradiated, then not very much of the body will be absorbing energy; the effect on the system as a whole will not be much. But if there is a big field on the skin, although the dose is still 100 r, the amount of absorption by the patient is very much more. Therefore, the size of the irradiation field is very important in considering dosage in x-ray therapy. If just a small field is used, in the course of a month a dose of several thousand roentgens may be given to that skin. Over a large field only a few hundred may be given and over the whole body less than one hundred can be used. That must be borne in mind in planning treatment. The sort of treatment given by the artificially radioactive substances is different. That is a whole body irradiation.

We cannot go into the matter of dosage calculations with these isotopes except to say that there is a formula by means of which these doses can be related to x-ray doses. The formula is very simple:

$$e. r. = 0.088 VT$$

It simply says that when one microcurie of radioactive isotope is deposited in 1 Gm. of tissue and remains there until its total disintegration, the "effective roentgens" or "equivalent roentgens" are equal to 0.088 times its half life in days times the energy of the beta particle in electron kilovolts. It is obvious that the longer the life for a given amount of material the greater will be the dose. Figuring that out for phosphorus and sodium, it will be seen that per millicurie of sodium the "e. r." will be much less than for phosphorus, since the life time is so different.

The beta ray energies are about the same. Sodium also emits gamma rays and this must be taken into account when thinking about dosage. Thus 25 millicuries of sodium produce about the same effect as 2.5 millicuries of phosphorus. It is evident that dosage cannot be calculated in millicuries without knowing about the life time and the radiations of the substance used.

DR. HENRY ARANOW, JR.: It might be interesting if we had an explanation of what the millicurie is.

DR. QUIMBY: The millicurie is that amount of any radioactive material such that  $3.7 \times 10^7$  atoms disintegrate per second. A microcurie is  $\frac{1}{1000}$  of that. A curie is 1000 times that. Initially the curie was the amount of radon which was produced by a gram of radium when the two were in equilibrium, and the unit has been taken over now to all artificially radioactive as well as naturally radioactive substances. It therefore is no measure of the total weight of material administered. If you have a curie (or millicurie) of a very short-lived material, you will get  $3.7 \times 10^{10}$  (or  $3.7 \times 10^7$ ) disintegrations at that instant, but the decrease in activity will be very rapid; while if you have a long-lived material you get the same activity at the instant and the decrease will be very slow. The result of that, as I said, is you can give a considerable number of millicuries of a very short-lived material but you have to be careful about giving very many millicuries of an element which is going to stay in the system for a long time.

At the University of California, radioactive phosphorus was one of the first substances made in any great quantity and therefore the substance investigated most assiduously. Among the studies made was the manner in which it was distributed through the living organism. It was found that radioactive phosphorus was deposited to a slightly greater extent in bone and bone

marrow, spleen and liver than it was in other tissues, not a great differential but one that could be noted.

That made Dr. Lawrence and his associates think that possibly by giving a dose of radioactive phosphorus which could be tolerated by the whole body, a differential radiation could be given to leukemic or lymphomatous cells. They started very cautiously with some leukemic patients and were very pleased with the results. The white counts went down, the platelet counts went up. Sometimes the spleen decreased in size. Symptomatically, the patients were much better. So they started to treat a series with planned therapy. Since then a number of other institutions have done the same sort of thing. The idea is this: The patient is given a dose of a phosphate in which a certain amount of the phosphorus is radioactive. This phosphorus then distributes throughout the body just as all phosphorus does. That means that radioactive atoms are incorporated in cells all through the body, just like normal phosphorus. They are normal phosphorus for all purposes as long as they stay phosphorus but every one of these atoms explodes at some time. In exploding, it shoots out beta particles which go through the cell in which it is deposited, and two or three adjoining cells. That irradiation goes on gradually, decreasing as the phosphorus is used up.

One millicurie of phosphorus distributed throughout the body means that 37 million phosphorus atoms are exploding every second. That sounds like a very big number until it is realized that 1 Gm. of tissue contains approximately one hundred billion billion atoms. Then 37 million does not seem so many. Of course explosions at that rate do not keep up. They get fewer as the phosphorus is used up at a rate of about 5 per cent a day, half in two weeks, half of what is left in two weeks, and so on. The

patient is subjected to a gradually decreasing universal bath of radiation.

In the spring of 1946 the group at St. Louis, Reinhart, Moore, Birnbaum and Moore, made a complete review of everything they could find in the literature on the use of radioactive phosphorus in this diseases and published it in the February, 1946 issue of the *Journal of Laboratory and Clinical Medicine*. Anyone who is interested in this subject should look over this report. It is very complete.

I will simply read you their conclusions. In myelogenous leukemia, there were 107 cases in the literature plus thirty-nine of their own. In the chronic form, all symptoms were relieved in 50 per cent; most of the symptoms in 85 per cent. Splenomegaly disappeared or was reduced in 64 per cent. They conclude that no cures and not even much relief was produced in acute and sub-acute cases. In chronic cases they made a comparison between the results of radioactive phosphorus, x-rays and Fowler's solution, and decided that the remissions produced were about the same. However, they say that therapy with radioactive phosphorus is pleasanter for the patient and there are no undesirable side effects—nothing like radiation sickness or toxic reactions which sometimes are produced by Fowler's solution. Therefore, only from that point of view do they consider it preferable.

In lymphatic leukemia there were 120 cases in the literature plus forty-five of their own. Of these eighty-four were chronic and seventy-one acute. They conclude that symptomatic relief in the chronic form is about the same as for the myelogenous type and that there is no help in acute lymphatic leukemia. They had no remission in their own group longer than one year; that is, after a year they had to give more treatment. The results are about the same as with x-rays. The treatment with radioactive

phosphorus is sometimes useful after *x*-rays have failed.

They report scattered results for other lymphomas. There are some specially good results in lymphosarcoma and particularly in reticulum-cell sarcoma. In Hodgkin's disease they report no improvement over *x*-rays. The series is very small and hard to evaluate.

Some time ago we were using radioactive sodium for some other purposes and the question arose: Could we not treat leukemia with that? Radioactive sodium is distributed uniformly through the extra-cellular body fluids. Therefore, a person treated with radioactive sodium would have a more homogeneous type of irradiation than with phosphorus. That is not any particular advantage. However, the life time of radioactive sodium is fifteen hours instead of fourteen days. That means that treatment could be better controlled because reactions could be observed more rapidly and doses followed more closely. A few patients have been treated and Dr. Evans will tell you the results. The series is not as large as the series for phosphorus. We did not expect any better results than with phosphorus but felt they should be as good.

There is just one other point which I should like to mention and that is the fact that these radiations are no respecters of persons. They would just as soon damage you as your patient if you give them a chance. Radiologists have had a horrible example for many years of what happened to the early radiologists who were not properly protected, and they are not going to get into trouble with these elements if they can help it. But there are a lot of people now coming into the field of radiation research and nuclear research who do not have that horrible example in the background. These little glasses of solution look very harmless. It is hard to believe if we pick up a jar of such material and carry it around for a few

minutes we may in the course of a couple of months have some very sore fingers. With beta ray products such as phosphorus, protection is relatively easy. An amount of lead or lead equivalent equal to about a millimeter will stop most radiations. But with gamma ray products the story is different. The gamma rays are extremely penetrating, and if any quantity is to be handled, before starting any routine, the only recommendation which I can give at the present time is to get in touch with the radiation physicist who can advise on necessary precautions. We certainly do not want any such tragedies forty years from now, as there were among people who forty years ago handled radium injudiciously.

DR. TURNER: I think that before asking for questions on the subject outlined by Dr. Quimby we might hear from Dr. Evans, who has had an intimate experience in the past few years with the treatment of patients with these agents.

DR. TITUS C. EVANS: Dr. Quimby and I have been working with Dr. Lenz on a study of the effects of radioactive sodium on patients with chronic leukemia. The patient drinks the radioactive sodium combined as sodium chloride in a very dilute solution which is practically tasteless. Within a short time the sodium is distributed throughout the blood and extra-cellular fluids. Organs containing much blood or other fluid containing sodium may receive slightly more radiation than the body generally but the general distribution of the sodium produces whole body radiation. Success, therefore, depends primarily upon the malignant cells being more radio-sensitive than normal cells. Since the half-life of radioactive sodium is about fifteen hours, a single dose will irradiate a patient with decreasing intensity over a period of two to three days. Loss of effective radiation through elimination is negligible. The radioactive sodium is measured in millicuries (mc) and the

amount administered each time depends upon body weight and condition of the patient.

We have treated two chronic lymphogenous leukemia cases which have been well controlled for approximately a year. The two cases were similar so I will discuss only one. The white blood count before treatment was approximately 70,000 and a small dose (10 mc) brought the count down to about 35,000 within a few days. After a week the count increased again, but another treatment brought the white blood count down to within normal limits. We have been able to keep the count below 20,000 for well over a year by a treatment every two or three months. Each treatment has been followed by improvement in the differential and an increase in the number of platelets.

The next patient to be discussed has chronic myelogenous leukemia. Before treatment the white blood cells were about 275,000. The spleen and liver were enlarged. Doses were increased from 15 mc to 35 mc before obtaining a drop in the count. The count is now within the normal range and the spleen and liver are no longer palpable. We have not observed any harmful effects of the radiation and these patients have suffered no discomfort.

One case of myelogenous leukemia has been more difficult to control. Dr Lenz had been able to control the disease for about a year with fairly heavy doses of *x*-rays. *X*-radiation in amounts necessary to be effective caused the patient considerable discomfort. We were able to bring the count down time after time with radioactive sodium without producing any ill effects. Regressions were only temporary and the spleen was gradually increasing in size, so that much heavier treatment was necessary to reduce the white blood count and the spleen size to normal. This amount of radiation did cause the patient to feel uncom-

fortable for a while. The patient says that the reaction was not as great as he had experienced with even moderate amounts of *x*-radiation. This is a rather stubborn case and I do not know how long it will be possible to continue treatment.

I will mention another case of myelogenous leukemia in which the results of treatment have not been too encouraging. This was a little girl of six in poor physical condition, and it was inadvisable to use heavy doses because of her anemia and low platelet count. It was possible to keep her fairly comfortable for about a year and also to obtain some improvement in the blood picture. The spleen, however, continued to enlarge, and she continued to grow weaker. At autopsy the spleen was found to be packed with malignant cells.

We have attempted therapy, with discouraging results, in terminal Hodgkin's disease, terminal lymphosarcoma, terminal lymphogenous leukemia and acute lymphogenous leukemia in children. In these cases some relief of pain and some improvement in blood picture was obtained but the progress of the disease was not affected.

One case of polycythemia vera has been studied. The patient was treated at weekly intervals for almost two months and has not been treated since that time (now over a year). Within three months after beginning treatment, the red blood cells had dropped from 8,000,000 to less than 5,000,000 and the hemoglobin had been reduced from 25 Gm. to less than 14 Gm. The blood picture has remained essentially normal up to the present time.

Use of radioactive sodium offers some advantages over *x*-ray treatment and possibly over radioactive phosphorus therapy. The use of radioactive sodium in therapy is limited, because of its short half-life, to institutions near the source of supply. Also, care must be exercised to avoid overexposure of the patient and the attending personnel.

DR. TURNER: We might pause here for a moment to ask if there are any questions about what Dr. Quimby and Dr. Evans said. I should like to ask one question and that is to what extent can a biochemical account be given of the effect of  $x$ -rays?

DR. QUIMBY: Perhaps some of the biochemists can answer that better than I can.

DR. TURNER: There has been increasing interest in the effect, for example, of chemotherapeutic agents on substrate competitors, enzyme inhibitors, and so forth and so on. Is there any information of that kind available with respect to the influence of  $x$ -rays?

DR. DEWITT STETTEN, JR.: Dr. Quimby, I do not have information on this point.

DR. EVANS: There have been attempts to pin down the fundamental effects of  $x$ -rays to enzymes breaking down large protein molecules to small ones, producing toxic substances, etc. Apparently such changes take place but to a limited extent and so many reactions occur at the same time that it is difficult to narrow the effect to any one thing. Enzymes have been thought to be sensitive to radiation, as they are under certain conditions, but in the cell it is a different problem. It is difficult to make a chemical study of this kind on a biological basis, although we can try it.

A DOCTOR: Is there any evidence that these radioactive elements can be so chemically combined as to increase the differential of absorption?

DR. QUIMBY: That is one of the things on which a great deal of work is being done. At the present time there has not been much success but many people are trying to find some means of making substances localize in particular types of tissue and in particular types of organs. If that is ever done, of course, there will be the possibility of local radiation from these substances. At the present the only example is iodine, which will localize in the functioning thyroid gland. If we can make other substances do

the same sort of thing for other regions, it will be fine.

DR. TURNER: We will go on to the subject of the chemotherapy of lymphomas. As you all know, Fowler's solution is one of the oldest chemotherapeutic agents which has stood the test of time. It has been employed in the treatment of leukemia and other types of lymphoma for about eighty years with such success that at times its usefulness approximates that of  $x$ -ray. It has been largely given up, however, because of untoward side reactions such as nausea, vomiting and diarrhea. One is not able to predict as satisfactorily that a therapeutic response will be obtained, whereas with  $x$ -ray therapy we are pretty familiar with what may be expected.

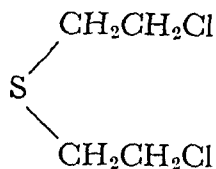
More recently, substances such as benzol and urethane have also been employed in the treatment of leukemias. Among the most interesting compounds which have been developed, largely as the result of work done during the war, are the nitrogen mustards, which have been used for perhaps three or four years.

Dr. Gilman of the Department of Pharmacology has been good enough to come up and tell us about some of the work on the nitrogen mustards.

DR. ALFRED GILMAN: I regret that the discussion on the nitrogen mustards was introduced as relating to the chemotherapy of lymphoma. Rather I think the contribution that these compounds have made to date is to point to fundamental mechanisms involving the cell nucleus, which are shared by  $x$ -ray, radioactive isotopes and the nitrogen mustards; the last mentioned, as far as we know, possess no type of radioactivity.

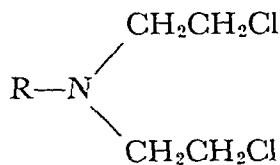
I would like to trace the story of the nitrogen mustards back to World War I, when sulfur mustard was so widely employed as a war gas.

Sulfur mustard has the following structure:



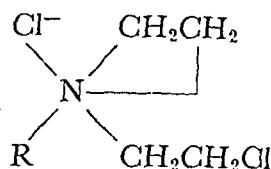
Sulfur mustard reacts with water eventually to replace the chlorine with hydroxyl, with the release of HCl. During World War I it was presumed that the effective action of mustard gas was due to the release of small amounts of hydrochloric acid within the cell. In retrospect it is difficult to imagine how such a theory could have been entertained, because the small amount of hydrochloric acid released would most certainly be readily neutralized and buffered by the cell. A few of the more astute observers noted that following extensive mustard lesions of the lungs, leukopenia often developed and was a grave prognostic sign. However, this observation was largely ignored, and between wars practically no studies were conducted on the effects of mustard on hemopoietic tissue.

With the advent of World War II, a new series of compounds was introduced, the nitrogen mustards, which differed only in that nitrogen replaced sulfur. Inasmuch as nitrogen is trivalent, there is room for one substituent group in the molecule. Following is the basic structure of the series of nitrogen mustards in which R represents the substituent group:



There was a background for appreciation of the chemical behavior of the beta-chloroethylamines because these compounds had been extensively studied. For example, it was known that in aqueous solution the beta-chloroethylamines undergo intramolecular cyclization as a result of a ring clouser

between the beta carbon and the nitrogen to form a quaternary ammonium base:



Whereas the original beta-chloroethyl group is very unreactive, the ethyleneimine group which is formed is one of the most reactive of organic structures. For example, it will react with a variety of biologically important chemical groupings such as amino, carboxyl, sulfhydryl, sulfide, phenolic, imidazole, organic phosphate, etc. In fact, any attempt to define the basic mechanism of action of the nitrogen mustards on the basis of chemical affinities is thwarted by the wealth of possible explanations.

The chemical reactivity of the ethyleneimine ring with biological compounds is of particular interest for the reason that the biological effects of the nitrogen mustards parallel and are almost identical in every respect with the biological effects of radiant energy. To emphasize this point, let us review briefly the effects of the nitrogen mustards on unicellular organisms and on the mammal.

Following the intravenous administration of nitrogen mustards in mammals, the first effects are noted in lymphoid tissue. In experimental animals one observes almost complete dissolution of lymphoid tissue within twenty-four hours. This is reflected in the peripheral blood by a severe lymphopenia. Similarly in human subjects following the injection of a few doses of nitrogen mustard, one may observe an absolute lymphopenia in the peripheral blood. There is also an effect on granulocytes, the degree of which is related to dosage. With a few doses of 0.1 mg. per kg. daily, one observes a moderate granulocytopenia. Increasing the number of doses results in a

more severe granulocytopenia. With ten daily doses the bone marrow is depressed to the extent that only occasional granulocytes are observed in the peripheral blood. Likewise, platelet formation is depressed. Again, the degree of thrombocytopenia is related to dosage. If one further increases the dose of nitrogen mustards in experimental animals, the effects now extend to the epithelial tissue of the gastrointestinal tract. Degenerative changes occur which eventually lead to a severe hemorrhagic enteritis. With still higher doses, there is evidence that every cell in the body is being affected. Animals run a progressive downhill course. Disturbances in water and electrolyte metabolism are outstanding. Severe diarrhea and vomiting contribute to anhydremia and circulatory collapse. In addition, the permeability of the cell membrane appears to be affected in that potassium is lost from and sodium enters the cell. It is not improbable that death results from the disturbance in water and electrolyte metabolism.

An even greater similarity between the effects of the nitrogen mustards and radiant energy is obtained when actions on cell nuclei are studied. For example, cleavage of sea urchin eggs is arrested. If male *Drosophila* are exposed to low concentrations of nitrogen mustard, chromosomal abnormalities result in as high a percentage of sex-linked lethals as has been observed with *x*-ray and ultraviolet radiation. The effect of mitosis is the same as *x*-ray: arrest does not occur at a particular stage but the cell goes on to complete its mitosis, after which, however, no further mitotic activity occurs. The details of the chemical and biological actions of the nitrogen mustards have been recently summarized.<sup>1</sup>

Investigators have been impressed with the fact that it is the tissues which are undergoing the most rapid rate of cell division that are the most susceptible to the action of

the mustards. Thus lymphoid tissue is particularly sensitive. It was only natural, therefore, that compounds which had such profound effects on lymphoid tissue should be evaluated in the therapy of lymphoma. Experimental work was cautiously started in 1942 at the New Haven Hospital. Preliminary reports of this and subsequent studies have appeared.<sup>2,3</sup> The results parallel those that can be obtained with *x*-ray. Perhaps the greatest success has attended the treatment of Hodgkin's disease. Remissions for varying periods up to eight months have been observed following single courses of treatment. Furthermore, favorable effects have been obtained in cases classified as roentgen ray resistant. There is some evidence that nitrogen mustard therapy may occasionally restore responsiveness to radiation. However, that resistance to the drug also develops is already evident.

In the treatment of lymphosarcoma the response is less predictable, but again similar to that observed with *x*-ray. Chronic lymphogenous leukemia appears to respond somewhat more favorably than chronic myelogenous leukemia but the results leave much to be desired. Little or no benefit is afforded in acute leukemia. In two reported cases of multiple myeloma, relief of bone pain was the only benefit noted.<sup>3</sup> Two patients with sympathoblastoma responded in a manner similar to *x*-ray.<sup>3</sup> Preliminary results in polycythemia rubra encourage further clinical trial.

With this brief analysis of the therapeutic results, I might say a few words as to the method of administration and the side reactions which occur. The nitrogen mustards are highly vesicant. They must be given intravenously and it is important that no extravasation occurs. They are most conveniently administered by injecting into the rubber tubing during the course of an intravenous drip of isotonic sodium chloride solution. The single dose is 0.1 mg. per kg.



body weight, but not to exceed 8 mg., given as a 0.1 per cent solution freshly prepared.

Local reactions at the site of injection are infrequent provided due precautions are taken, but occasionally thrombophlebitis develops. Nausea and vomiting are not uncommon, usually occurring two to three hours after injection and subsiding within the next few hours.

The first patients to receive nitrogen mustards were treated much too vigorously (ten daily doses) and exhibited severe granulocytopenia and thrombocytopenia. By reducing the total number of doses to three or four, given daily or every other day, it is possible to obtain an adequate therapeutic response without too severe a reaction on the bone marrow. However, a moderate degree of granulocytopenia and thrombocytopenia is always to be expected. A minor anemia may also develop.

The nitrogen mustards have introduced many more problems than they have solved. One of the most intriguing is the possible basic relationship between the actions of the nitrogen mustards and x-ray on the cell nucleus. They are so similar that one is led to believe that they must have some mechanism of action in common.

Another intriguing problem, especially from the pharmacological point of view, is the fact that the nitrogen mustards represent not one but rather a series of compounds of almost infinite number. Those that have been explored to date were developed as chemical warfare agents and therefore represent the most toxic members of the group. By changing substituent groups one can markedly affect distribution, reactivity, toxicity, and other important properties. Thus we have a means by which higher specificity of action within this series may be obtained.

The problem of combined therapy with nitrogen mustards, x-ray and radioactive isotopes still remains to be investigated.

There have been a few instances where patients, resistant to radiation responded to nitrogen mustard. Subsequently their sensitivity to radiation returned. There have also been isolated cases where patients have been resistant to nitrogen mustard but sensitive to radiation. Thus there is the possibility that alternate therapy with nitrogen mustard and either x-ray or radioactive isotopes may solve the problem of resistance in the treatment of lymphoma. The principle of alternating therapeutic agents to prevent "fastness" in the chemotherapy of infectious disease is well established. A similar opportunity is now presented in the treatment of lymphoma.

There is another point of interest in this connection. The nitrogen mustards are so reactive that their effects are over within a matter of minutes. Thus whatever happens subsequent to their injection is the result of reactions which occur over a very brief period of time. This has been beautifully demonstrated by H. Smith and his co-workers who occluded the circulation to a given area for a period of five minutes after the injection of nitrogen mustard. Complete protection could be afforded to the bone marrow or the gastrointestinal tract by this technic. Therefore, the possibilities of combined treatment with radioactive compounds are intriguing in that with the nitrogen mustards one can get an initial effect which may be maintained with radioactive isotopes.

These are only a few of the problems which come to mind. In the clinical application of the nitrogen mustards we have gone only a short way in defining dosage and the courses of treatment that are best suited for a few syndromes. Biological investigators are little more advanced. At the present stage of their development, I would like to look upon the nitrogen mustards as a challenge to the clinician and biologist, the latter better to define their basic mechanism of action

and the former better to define therapeutic applications. To the pharmacologist is assigned the responsibility of forging a more potent chemotherapeutic weapon that may overcome the present limitations of this group of chemical warfare agents which has found therapeutic applications.

DR. TURNER: Are there any questions on this subject?

STUDENT: Has there been enough time to establish whether the cells tend to show less and less effect of treatment on protracted therapy? That occurs with *x-ray*.

DR. GILMAN: Yes, there has, and the response tends to become less marked with successive courses, but there again the possibility of alternating between radiant energy and the nitrogen mustards is opened up.

SAME STUDENT: Or alternating with different nitrogen mustard compounds?

DR. GILMAN: Or different compounds, possibly.

STUDENT: Has the effect of the nitrogen mustards on enzyme systems been studied?

DR. GILMAN: Yes, a variety of enzyme systems has been investigated. The most marked effects are exerted against the phosphokinases and indeed the British believe that this may represent the basic mechanisms of the vesicant action of this type of compound. However, it would be premature to attribute the actions of the nitrogen mustards on nuclear mechanisms to a specific enzymatic lesion.

#### SUMMARY

The term 'lymphoma' is applied to a variety of new growths having in common involvement of the spleen and lymph nodes but not otherwise known to be related. In Hodgkin's disease the lesion appears morphologically to resemble in many respects an infectious granuloma because of the variety of cell types involved; yet all efforts to demonstrate an etiological agent have so far failed. With the development of experi-

mental animal technics in recent years, controlled investigations into this group of diseases may yield further information valuable to cancer research.

Radioactive isotopes and the nitrogen mustards have recently been introduced as agents of promise in the therapy of diseases of the lymphoma group. Isotopes of elements are atoms which have the same number of protons but differ in the number of neutrons in their nuclei, in accordance with their atomic weight. Hydrogen and heavy hydrogen are simple examples of this. The elements are distinguished by an ordered increase in the number of nuclear protons, in accordance with their atomic number. Hydrogen has only one proton, helium has two, lithium has three. As the atomic nucleus becomes more complex it also becomes more unstable. Natural substances with atomic numbers above 83 are so unstable that they undergo spontaneous nuclear disintegration by ejecting portions of their nuclei, a phenomenon called radioactivity. When atoms of substances below the atomic number of 83 are bombarded with nuclear particles from an outside source such as the cyclotron, a small number of normally stable atoms may take up extra particles in their nuclei. This produces an unstable nucleus which at some time breaks down with emission of alpha, beta or gamma radiation. This process is artificial radioactivity and such atoms are artificial radioactive isotopes.

Obviously, not all of the radioactive isotopes disintegrate in the same fashion or in the same length of time. But these factors are important ones which must be taken into account in order to calculate the amount of radiation given off and to estimate the dosage to be used. For the radioactive isotopes the unit of measure is the *millicurie*, or that amount of material which will insure the disintegration of  $3.7 \times 10^7$  atoms per second. *X-ray* dosage, on the

other hand, is expressed in terms of *roentgens*. While these are different standards of measure, they may be correlated by the equation  $e.r. = 0.088 VT$ .

The nitrogen mustards developed during World War II are highly interesting compounds which seem to mimic the biologic effects of radiant energy. Lymphoid and granulocytic cells appear to be most sensitive to their action, then platelets, epithelial cells and other types in descending order of sensitivity. The remarkable similarity in results when cell nuclei are exposed either to irradiation or to the nitrogen mustards is striking. How either agent produces its effects is completely unknown.

The nitrogen mustards are highly vesicant. They must be surely placed within the vein, cause occasional thrombophlebitis nevertheless with nausea and vomiting, and in toxic doses, granulocytopenia, thrombocytopenia and anemia. When carefully administered they seem to produce about the same results in the lymphoma group as does irradiation. There is hope of increasing organ or system specificity by the proper use of substituent groups in the molecule.

Also, they offer perhaps the most easily manageable form of therapy yet known in this group of disease. There is the further possibility that they may be combined with radiotherapy to achieve results beyond those so far obtained by either method alone.

Myeloid and lymphatic leukemia of the chronic types do well with either form of therapy. Acute leukemia, however, appears to be no more satisfactorily managed by the substances under discussion, than with the usual  $x$ -ray therapy. About the same may be said of Hodgkin's disease and the lymphosarcomas. Polycythemia on the other hand does well with the isotopes and gives indications of responding favorably to the nitrogen mustards.

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# Clinico-pathological Conference

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## Acute Meningitis\*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a forty-three year old white married housewife who entered the Barnes Hospital for the first time on August 5, 1946. She was stuporous on admission and the history was obtained from her husband who stated that the patient's chief complaints were headache and fever. The family history was non-contributory. Except for smallpox many years previously, the patient had had no other illnesses or operations and had enjoyed excellent health. She had had no known recent exposure to an acute infectious disease.

Three weeks prior to admission, while vacationing in Michigan, she developed a fine red rash over the arms. No other symptoms were present at the time. Benadryl was prescribed by a physician who saw her and the rash disappeared within a few days. One week later the patient complained of headache and a severe pain between the shoulder blades. There was accompanying general malaise and her temperature was noted to be 101°F. Concomitantly a furuncle developed in the left upper lumbar region. The patient's symptoms persisted and seven days before entry to the Barnes Hospital, she was admitted to a hospital in a rural community in Illinois. A report from the physician who attended the patient there stated that on examination ptosis of

the right eye and stiffness of the neck were observed.

Laboratory studies included normal white blood cell and differential counts. The urinalysis was normal. The patient was treated with penicillin and a sulfonamide but her temperature continued to rise to 103°F. daily. The furuncle enlarged in size but did not become fluctuant. The white blood cell count remained normal. Agglutination tests for typhoid fever, undulant fever, tularemia and typhus fever were negative. A roentgenogram of the chest showed nothing abnormal. On August 1, 1946, a lumbar puncture was performed. The spinal fluid was clear and contained five cells; a differential count was not reported. The patient failed progressively; ptosis of the right eye increased, stupor became deeper and the neck became stiffer. A second lumbar puncture was performed on August 5, 1946. Eighty-seven cells were present and all were lymphocytes. A Pandy test was positive; 100,000 units of penicillin were instilled intrathecally. A repeat chest roentgenogram showed the lung fields to be clear, but "the diaphragm was elevated suggesting a lesion beneath it." Because of the lack of response to therapy, the patient was transferred to the Barnes Hospital.

On entry her temperature was 39.6°C., pulse 110, respirations 24 and blood pres-

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sure 130/80. The patient was moderately obese, semi-stuporous, disoriented and resistant to examination. Her speech was uninterpretable. The skin was clear, except for a pigmented area the size of a silver dollar over the left upper flank. The head showed no evidence of trauma. There was ptosis of the right eye. The pupils were round; the left was slightly larger than the right but both reacted slightly to light. The patient could not look to the right as well as to the left. Examination of the fundi showed an area of old choroiditis on the right but no other abnormalities. There was thickening of the left ear drum. The pharynx could not be seen because the jaws were held rigid. The neck was rigid. Examination of the lungs revealed no abnormal findings. The heart was not enlarged and the rhythm was regular. A soft, Grade II, systolic murmur was heard over the precordium. The abdomen was soft; tenderness was noted in the epigastrium and left upper quadrant. Exquisite tenderness was elicited in the left costovertebral angle. The right arm was not used as well as the left. Abdominal reflexes, knee jerks and ankle jerks were not obtained. Bilateral Kernig signs were present. There were no pathological toe signs.

The laboratory data were as follows: Blood count: red cells, 5,770,000; hemoglobin, 16.1 Gm.; white cells, 15,500; differential count: eosinophiles, 1 per cent; stab forms, 13 per cent; segmented forms, 68 per cent; lymphocytes, 10 per cent; monocytes, 8 per cent. Urinalysis: albumin, trace; sediment, occasional granular cast. Kahn test: negative. Non-protein nitrogen: 26 mg. per cent. Blood culture: no growth.

Shortly after admission a lumbar puncture was performed. The initial pressure was 275 mm. of water; the final pressure, 125 mm. The fluid was xanthochromic. There were 270 cells without acid, many of which were crenated red blood cells; with

acid there were 54 cells of which 22 were polymorphonuclear leukocytes and 34 were lymphocytes. No sugar was present in the fluid. The Wassermann test was negative and the colloidal gold curve was 1111111000. The fluid was sterile on culture. No pellicle was observed after two hours. Insufficient fluid was obtained for accurate protein determination but it ranged between 600 and 800 mg. per cent.

The patient was given intravenous fluids and closed urinary drainage was established. On the day after admission the neurological findings remained unchanged but tenderness was noted over the entire left abdomen. Because the same response was obtained from pinching the skin as on deep palpation, it was thought that the tenderness possibly represented superficial hyperesthesia. The patient's temperature remained high. The white blood cell count rose to 16,800, the differential showing 9 stab forms, 71 segmented forms, 10 lymphocytes and 10 monocytes.

On the third hospital day another lumbar puncture was performed. The initial pressure was 350 mm. of water; 14 cc. of clear yellow fluid was withdrawn and the final pressure was 150 mm. of water. Without acid 300 cells were present, of which a few were crenated red cells. With acid there were 270 cells, 50 per cent being polymorphonuclear forms and 50 per cent lymphocytes. The protein was 800 mg. per cent, sugar, 19 mg. per cent, and chlorides, 380 mg. per cent (626 mg. per cent as NaCl). The fluid was again sterile on culture. A pellicle developed in the spinal fluid; a hanging drop preparation showed no torula bodies. Smears of the pellicle were stained for acid fast bacilli but none were found.

The patient became more stuporous; her temperature rose to 40.8°C. Her respirations were shallow, forced and very rapid at 46 per minute. Examination of the lungs

revealed that breath sounds were diminished at both bases, more so on the left. Marked tenderness in the left upper abdomen persisted, and there was a suggestion of muscle guard. The patient's urinary output was fair. Reexamination of the eye grounds showed them to have remained unchanged. The patient's condition deteriorated rapidly, her arms and legs became cold, she became cyanotic, and she expired on August 8, 1946.

#### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is a very dramatic one. A woman, forty three years of age, whose general health had been excellent, became acutely ill, apparently with some type of meningitis, while enjoying a summer vacation. She died about two weeks later. The history records that three weeks before her death she developed a skin eruption for which she was given benadryl. In a few days, either because of the benadryl or spontaneously, the rash disappeared. It is true that benadryl does effect the urticarial type of lesion which is so common in the summertime. The first question to be asked is: Was there any relation between the eruption and her subsequent course? I feel that there was not for there was an interval of approximately one week after the disappearance of the rash and the onset of the more serious symptoms during which the patient felt well. If we conclude that the rash was incidental, it can be said that her illness began about July 24, 1946, two weeks before her admission to the Barnes Hospital. She complained of headache, fever, malaise and pain between the shoulders. She entered a hospital in rural Illinois where very thorough studies were made. The findings included a stiff neck, ptosis of the right eye, and a large furuncle in the left flank. Dr. Wood, do you believe that the neurologic findings and the furuncle were

part of the same process, or do you think they were unrelated?

DR. W. BARRY WOOD, JR.: I believe that they were probably not related. It seems more likely that the meningeal reaction was on a basis other than that of staphylococcal infection which produced the furuncle. It is quite possible that the lesion in the central nervous system was an abscess which lay adjacent to the meninges and gave rise to a meningeal reaction. I do not believe, however, that the evidence indicates that this patient had staphylococcal meningitis.

DR. ALEXANDER: If this was an abscess, it apparently was not large because the fundi were normal even on the day before death. Would you comment on the spinal fluid findings, Dr. Moore, in regard to the possibility of a brain abscess? It is noted that in the hospital in Illinois, the spinal fluid obtained at the time of the second lumbar puncture revealed 87 cells of which all were lymphocytes. Would such a total and differential count be in keeping with the diagnosis?

DR. CARL V. MOORE: In the very early stage of an abscess perhaps, for at that stage the changes in the fluid may be variable and it is conceivable that lymphocytes would predominate. Usually, however, when there is irritation of the meninges because of an abscess, the percentage of polymorphonuclear leukocytes eventually rises.

DR. ALEXANDER: If we are to consider the furuncle of no importance in regard to the symptoms in the central nervous system, what, in your opinion, is the most probable diagnosis?

DR. C. V. MOORE: The very high spinal fluid protein is striking and on one occasion the spinal fluid sugar was zero. In meningismus, the spinal fluid is sterile and it is rare for the spinal sugar to be that low. If one were to rely on the experience accumulated by Merritt and Fremont-

Smith, he would arrive at the conclusion that this process was an infectious one which probably involved the spinal fluid even though organisms were not recovered.

DR. WOOD: According to work being carried on by Mr. Goldring, one of our senior students, there is experimental evidence that the presence of polymorphonuclear cells in the subarachnoid space will not bring the sugar down in the intact animal, although in vitro, the sugar may be lowered considerably by leukocytes. Apparently, in the intact animal, sugar enters the spinal fluid continuously and in the studies carried out to date, it has been impossible to lower the spinal sugar significantly by merely producing an inflammatory reaction in the subarachnoid space by the use of non-specific irritants.

It should be emphasized that this patient was given 100,000 units of penicillin intrathecally. Prior to instillation the spinal fluid cells were all lymphocytes. Such a dose of penicillin intrathecally is extremely large. 10,000 units is the dose usually recommended and 20,000 units is the upper limit. Some of the changes in the spinal fluid in this case may have been due to the large amount of penicillin introduced intrathecally.

DR. C. V. MOORE: Could the crenated red cells and the xanthochromic fluid be explained on that basis, Dr. Wood?

DR. WOOD: Possibly. There may have been sufficient injury to the capillaries in the subarachnoid space to allow passage of both protein and red blood cells into the cerebrospinal fluid.

DR. PAUL O. HAGEMAN: The xanthochromia may have been due to the color of the penicillin.

DR. ALEXANDER: Your suggestion as to the explanation of the xanthochromia fails to account for the fact that the red cells in the spinal fluid were crenated. Does xanthochromia occur in the spinal fluid in tuberculous meningitis?

DR. HAGEMAN: Yes.

DR. ALEXANDER: The spinal fluid chlorides were reported as 380 mg. per cent. Dr. Fletcher, is that figure a little low?

DR. PALMER H. FUTCHER: 436-454 mg. per cent is the normal range for spinal fluid chlorides; they are thus slightly higher than the normal serum chlorides. In this case the spinal fluid chlorides were low.

DR. ALEXANDER: The combination of the spinal fluid findings here, low sugar, low chlorides, increased cell count with lymphocytes ranging from 50 to 100 per cent and a pellicle on standing is strongly suggestive of tuberculous meningitis.

DR. C. V. MOORE: I agree, but no organisms were found in the pellicle. Further the sugar of zero is not adequately explained, unless it fell as a result of the irritation of the penicillin.

DR. ALEXANDER: Do you consider the subsequent figure of 19 mg. per cent compatible with the diagnosis?

DR. C. V. MOORE: Yes.

DR. JOHN R. SMITH: Given one milliliter of spinal fluid containing many white cells, how long approximately will be required for the sugar to disappear?

MR. SIDNEY GOLDRING: In vitro, 10,000 cells per milliliter can reduce normal sugar values to zero within two hours. In this case the cell count was too low to be solely responsible for reducing the sugar.

DR. ALEXANDER: If this patient did not have tuberculous meningitis, what type of meningeal irritation or meningitis may give rise to a lymphocytosis in the spinal fluid and the neurologic findings recorded here.

DR. HAGEMAN: I believe that the clinical picture may have been due to staphylococcal sepsis; the findings are compatible with those which would result from an abscess adjacent to the meninges.

DR. WOOD: Where would such an abscess be located to give rise to the neurologic findings that this patient exhibited? These in-

cluded ptosis of the right eyelid, weakness of the right arm and sensory changes on the left, probably hyperesthesia.

DR. ALEXANDER: The hyperesthesia may have been a sequela of the furuncle for it was very extensive. Unfortunately a complete sensory examination was not recorded and it was merely noted that pressure over the left side of the abdomen caused a good deal of discomfort.

DR. WOOD: Dr. Hageman, are you considering a lesion in the left motor cortex?

DR. HAGEMAN: Yes.

DR. WOOD: The diffuse neurologic signs, particularly the ptosis, are difficult to explain on the basis of a cortical lesion. On the other hand if the third nerve was involved by meningitis, the ptosis could be explained. Third nerve lesions are commonly seen by the syphilologists; perhaps Dr. Scott can comment on the possible relationship of a cortical lesion to third nerve palsy.

DR. VIRGIL C. SCOTT: I do not believe that third nerve palsy can be explained by a cortical lesion.

DR. WOOD: Do you agree that a lesion in the meninges would explain the cranial nerve lesion?

DR. SCOTT: Yes.

DR. WOOD: I believe this point constitutes the strongest evidence in favor of the diagnosis of meningitis.

DR. ALEXANDER: Is third nerve involvement common in tuberculous meningitis?

DR. WOOD: Yes.

DR. FUTCHER: Dr. Alexander, is it not true that the white blood cell counts of only 7,600 and 8,000 recorded during the first part of the patient's illness, are against the diagnosis of staphylococcal infection. Certainly if there was staphylococcal bacteremia and a metastatic abscess in the brain, the white count should have been much higher.

DR. WOOD: That is a good point.

DR. ALEXANDER: Is tuberculous meningitis common in a patient in this age group?

DR. ROBERT A. MOORE: Tuberculous meningitis is certainly far more common in children than in adults.

DR. ALEXANDER: The course of the illness in this patient was two weeks; that seems very rapid for tuberculous meningitis.

DR. HAGEMAN: It is shorter than the usual course by at least fifty per cent.

DR. WOOD: Perhaps the rapid course could, in part, be accounted for by the additional meningeal irritation resulting from the large amount of penicillin which was introduced intrathecally.

DR. ALEXANDER: This patient had two chest roentgenograms which were said to have shown no evidence of tuberculosis. It is likely that she had a subcortical lesion which ruptured into the subarachnoid space.

DR. HENRY A. SCHROEDER: Although this course would be a rapid one for torulosis, the lesions in that disease may involve both the skin and the central nervous system and there may be similar spinal fluid findings.

DR. WOOD: What was the hospital diagnosis?

DR. ROBERT J. GLASER: The admission diagnosis was brain abscess but in view of the subsequent findings the final clinical diagnosis was tuberculous meningitis.

DR. WOOD: Bronchopneumonia would perhaps explain the leukocytosis which occurred terminally; it was not in keeping with tuberculous meningitis.

DR. ALEXANDER: It would appear that the consensus of opinion expressed in the discussion favors the diagnosis of tuberculous meningitis.

*Final Clinical Diagnosis:* Tuberculous meningitis.

#### PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: At autopsy the body was that of a well nourished adult white woman. The significant findings were in the brain, the lung, and the adrenal



FIG. 1.

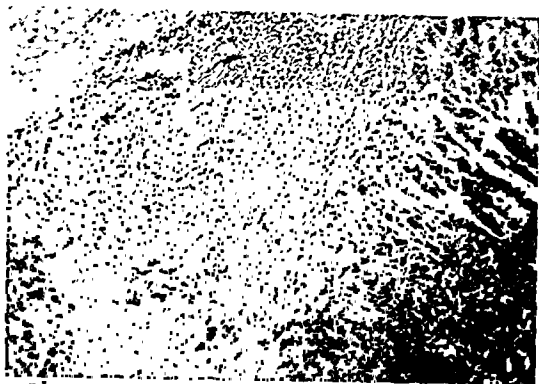


FIG. 2.

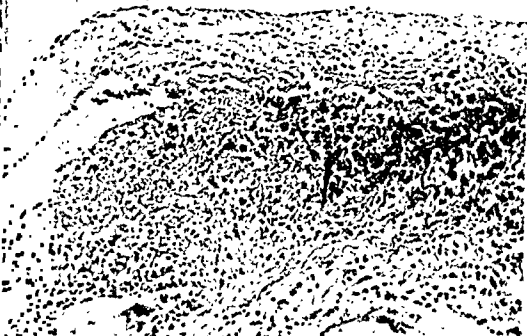


FIG. 3.



FIG. 4.



FIG. 5.

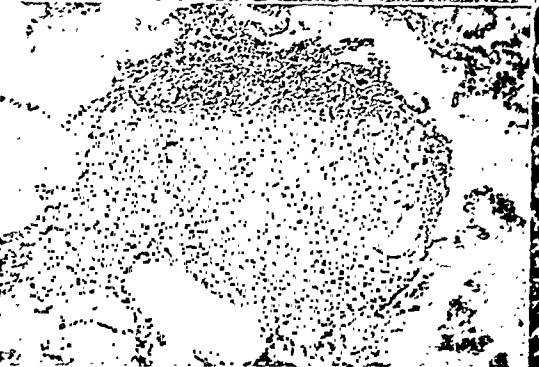


FIG. 6.

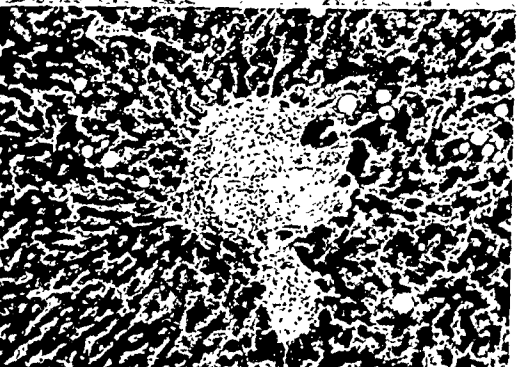


FIG. 1. Section of the right adrenal gland showing caseation necrosis extending through the cortex and involving periadrenal fat.  $\times 100$ .

FIG. 2. Section of the meninges showing caseous necrosis of the exudate.  $\times 100$ .

FIG. 3. Section showing characteristic changes of tuberculous meningitis involving a vessel in the meninges.  $\times 100$ .

FIG. 4. Section through a meningeal vein in the wall of which a tubercle may be seen.  $\times 100$ .

FIG. 5. Section of the lung showing early tubercle formation.  $\times 470$ .

FIG. 6. Section of liver showing fibrous nodule, possibly a healed tubercle.  $\times 470$ .

glands. The right adrenal weighed 22 Gm. and the left 5 Gm. The medullary portion of the right gland was completely replaced by yellowish-white, firm, cheesy material. In only one area, one cm. in diameter, it passed through the cortex, destroying the latter, and lay in apposition to the periadrenal fat. The medullary portion of the left adrenal gland was similarly involved.

The brain on gross examination showed slight opacity of the meninges over the base, extending from the optic chiasm back to the posterior edge of the pons. No tubercles were seen along the vessels in the Sylvian fissures or on the surface of the cerebellum. Multiple sections through the brain after fixation revealed no caseous foci similar to those seen in the adrenal glands. The left

lung was firmly bound to the parietal pleura by filmy fibrous adhesions which were easily broken. A fibrous pleural scar was noted in the apical portion. The right lung showed a few pleural adhesions. A calcified nodule was present in the periphery of the lower lobe and a cluster of calcified nodules in a bronchial lymph node. In the dependent portions of the lung, especially in the lower lobes, there were multiple, depressed, rubbery, purple foci which were interpreted as areas of atelectasis; in addition, diffusely throughout there were small, red, elevated foci, rather firm with a central yellow dot, interpreted as bronchopneumonia around the small bronchi.

DR. ROBERT A. MOORE: Dr. Johnson has presented to you our findings at the time of autopsy; in each adrenal gland there was a tuberculous process involving the medulla to a greater extent but extending out at one site into the cortex of the gland. In the meninges there was an inflammatory process which had led to increased opacity, but a diagnosis of tuberculous meningitis could not be made with any degree of certainty on the basis of the gross examination for the two most characteristic findings were lacking: the thick translucent type of exudate at the base of the brain, and the presence of numerous small tubercles throughout the meninges. In general, the diagnosis of tuberculous meningitis can be made if either one or both of these changes is observed.

In the microscopic study of the case, the first significant section (Fig. 1) is from the right adrenal gland where caseation necrosis is seen, extending through the cortex to involve the capsule and periadrenal fat. In the wall of the vein which lies outside the capsule, there is beginning necrosis. There is a fibrin thrombus occluding the lumen of the vessel. This finding is possibly of significance in explaining the pathogenesis of the meningitis, in view of Bateson's recent studies on the vertebral veins and their com-

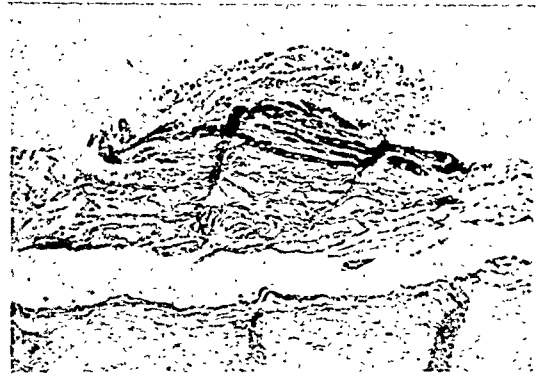


FIG. 7. Section from the right eye showing an area of chronic choroiditis.

munications. In Figure 2 a section of the meninges is seen showing the arachnoid membrane, the subarachnoid space, and a portion of the brain; there is early caseation necrosis of the exudate in which most of the cells are mononuclear forms. Although the lesion is fairly characteristic the diagnosis of tuberculosis can not be made with certainty. In the next slide (Fig. 3) a more typical lesion of tuberculous meningitis is observed as evidenced by the formation of so-called tuberculous granulation tissue around the vessels in the meninges. The lesion is early for the epithelioid cells have a foamy type of cytoplasm and are not yet arranged radially about the vessel. Threads of fibrin are present in the subarachnoid space. The next section (Fig. 4) shows an excellent example of a tubercle in the wall of a meningeal vein. There is cellular infiltration and the tubercle projects directly into the lumen. There were several similar examples in other sections taken from the meninges.

A few early tubercles, composed of epithelioid cells, were scattered throughout the lungs. Giant cells had not yet formed, and the epithelioid cells were not yet organized into a well defined tubercle. (Fig. 5.) The gross diagnosis of bronchopneumonia was confirmed by microscopic study. A section of liver (Fig. 6) shows one of the lesions which were seen. There were nodules of fibrous tissue without epithelioid or giant

cells. They may be interpreted as healed tubercles.

Sections were stained for acid fast bacilli; organisms were seen in the adrenal gland and the meninges.

At the time of autopsy we were asked to remove a posterior segment of the right eye where a pigmented scar in the choroid was diagnosed as chronic or healed focal chorioiditis. The microscopic section of that lesion (Fig. 7) confirmed the diagnosis.

The pathologic anatomy in this case is fairly evident. The calcified nodule in the periphery of the right lower lobe together with the calcified nodules in the tracheo-bronchial lymph nodes are generally accepted as evidence of primary tuberculous infection. The fibrous scar in the pleura of the apex of the left lung is not considered, in itself, to be of tuberculous origin unless associated with parenchymal involvement. In the adrenal glands there was active caseous tuberculosis with tubercle bacilli readily demonstrable. In the brain, tuberculous meningitis of an acute character, not fully developed, was present; it was consistent with a duration of two or three weeks. In the liver, there were a few tiny fibrous scars, interpreted as possible healed tubercles. The

absence of similar lesions in the spleen, however, throws doubt on the interpretation.

With regard to pathogenesis, I do not know what the significance of the vertebral veins is in this situation. The accepted explanation for development of tuberculous meningitis is rupture, into the meninges or ventricular system, of a tuberculoma lying in the substance of the brain. Such a lesion could not be demonstrated in this case. In our experience, it has often been difficult to demonstrate a tuberculoma. The communication of meningeal and systemic venous channels through the elaborate network of vertebral veins described by Bateson offers an alternate pathway for extension of the tuberculous process.

*Final Anatomic Diagnoses:* Caseous tuberculosis of both adrenal glands; tuberculous meningitis; miliary tubercles in the lungs; bronchopneumonia, slight; focal atelectasis of the lungs; calcified nodules in lower lobe of right lung; calcified nodule in a right bronchial lymph node; fibrous pleural scar in apex of right lung; small pigmented nodule in fundus of right eye and brown pigmentation of skin in left lumbar region (history of furuncle seventeen days prior to death).

# Case Report

## Prostigmine Therapy in Hemiplegia\*

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and LEONARD I. LAPINSOHN, M.D.

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**T**HIS case report appears of interest because it seems to add weight to the suggestion that prostigmine represents an added therapeutic aid in the treatment of paralysis due to vascular accidents. In addition, it affords interesting speculative material relative to the theory that the nerve impulse is associated with, if not originated by the interaction of acetylcholine with other physiological components of the nervous mechanism.

### CASE REPORT

On February 15, 1946, the patient, a white female, age thirty-nine, was admitted to the Jewish Hospital with the diagnosis of a recent cerebral vascular accident. A history of a rather marked hypertension covering a period of five years was obtained. About two and a half years prior to admission the patient awoke from an apparently sound sleep complaining of numbness in the left side of her face and weakness in her left arm. Following treatment for this condition she eventually regained full control of her limb. She was apparently well following this episode until her present illness, except for some varying degree of headache, nervousness, fatigue, and constipation, which her family physician attributed to hypertension.

On the night of admission the patient, becoming excited during a card game, complained of feeling generally ill and of numbness and tingling on the right side of her body. She became semi-stuporous and finally lapsed into complete unconsciousness, developing a flaccid paralysis of the right side of her body.

Physical examination revealed a well nour-

ished female, with stertorous respiration, flushed face, confused and semi-stuporous. The heart sounds were increased in intensity, sinus tachycardia was present, and moderate left ventricular enlargement was elicited on palpation and percussion. There were no murmurs or thrills present. The eyes reacted to light but the left pupil was larger than the right and a conjugate deviation of the head and eyes to the left was noted. A central facial palsy was present. Flaccid paralysis of the right upper and lower extremity was present, with hyperactive deep and superficial reflexes in the upper, and absent reflexes in the lower extremity. There was slight nuchal rigidity and a suggestive Kernig sign. Spinal tap revealed a bloody spinal fluid with a pressure of 350 mm. of H<sub>2</sub>O. The blood pressure on admission was 250/150, temperature 98.2°F., and the pulse and respiratory rates were 120 and 25 per minute, respectively.

Phlebotomy was performed on admission, with the removal of 400 cc. of blood. The blood pressure after phlebotomy was 180/140. Removal of 10 cc. of spinal fluid over a period of fifteen minutes caused a drop in spinal fluid pressure from 350 mm. to 90 mm. of H<sub>2</sub>O. Following phlebotomy and spinal tap, the patient appeared to become more alert although still semi-stuporous. Dehydrating enemas and 50 per cent glucose, intravenously, were employed as indicated by signs of increased intracranial pressure. Further medication consisted of sodium nitrite, gr. iss, aminophylline, gr. iii, and phenobarbital, gr. ss four times a day. An electrocardiogram revealed no evidence of myocardial damage and eye ground examination revealed moderately advanced arteriosclerotic changes. The patient's course was a

\* From Jewish Hospital, Phila., Pa.

stormy one from the time of admission to five days following her cerebral accident. She remained semi-stuporous, did not react well to stimuli, and her prognosis appeared to be extremely grave. On the sixth day following her admission, the patient became more alert, was able to recognize visitors and appeared to be improving somewhat. Her general condition improved greatly during the following week, but while the patient's prognosis as to survival steadily improved, there was no evidence of improvement in the movement of her paralyzed limbs, the physical signs remaining approximately the same as on admission. Nineteen days following admission there was still little or no improvement in the movement of her paralyzed limbs.

Barnes and Beutner<sup>1,2</sup> have suggested that cholinergic drugs should theoretically stimulate healing of central nervous system lesions. Ward and Kennard employed doryl in primates.<sup>9</sup> Jepson suggested the use of prostigmine in the treatment of infantile cerebral paralysis. It was decided to employ prostigmine in this case in an endeavor to hasten the restoration of limb function. Thirty mg. of prostigmine bromide with  $\frac{1}{150}$  gr. of atropine sulfate were administered three times a day starting on March 5th, approximately nineteen days after admission. There appeared to be marked improvement in the patient's condition with increase of range of motion, which was manifested within twenty-four hours. However, nausea, abdominal cramps, and diarrhea supervened, whereupon atropine sulfate, gr.  $\frac{1}{100}$ , was administered which immediately relieved these symptoms. Prostigmine was discontinued for a day following this episode, and there seemed to be a regression in range of motion, strength and coordination of voluntary movement of the upper and lower limbs. The dose of prostigmine was then reduced to 15 mg. four times a day and  $\frac{1}{2}$  gr. of phenobarbital was added to each dose, on the theoretical supposition that the latter drug would act as a depressant of any further untoward reactions.\* This dosage appeared to cause no

untoward reaction and the patient's condition rapidly improved. On March 10th she was able slowly to flex and extend her lower extremity and to raise her arm to an angle of 15 degrees, and lift it approximately two inches from the flat surface of her bed. Her seventh and twelfth nerve palsies were greatly improved. On March 11th the ability to flex and extend her leg partially increased in strength and speed of execution; she became able to touch her right finger to her nose, her grip became stronger and coordination improved greatly. On March 12th she was able to place her hand on the top of her head, and slowly flex, extend, abduct and adduct, pronate and supinate her right arm. Her speech and vision were also improved. On March 13th she was able completely to flex and extend her leg to an angle of 60 degrees against gravity in a sitting position, able to throw a ball, and her vision and speech were normal except for a slight nasal quality to her voice. On March 14th her condition was approximately the same. Her speech was somewhat less nasal in quality, and her right thumb and fingers appeared less spastic, and better coordinated. On March 16th she was able to turn from side to side in her bed. On March 17th she was allowed to sit in a chair by her bed for a half hour. On March 18th the patient attempted to stand, and on March 19th she was able to take a few steps. Her condition after this improved gradually until eight weeks after her discharge from the hospital on March 20th, she appeared to be clinically well except for slight weakness of her right arm, and a slight lack of coordination in her gait. Prostigmine was continued during her convalescence in the doses employed during hospitalization, and a close watch was kept on her progress during this period. Follow-up examination reveals that this patient has made a rather unusual recovery, in view of the severity of her cerebral accident and her poor prognosis on admission.

Of interest, also, in this case, is the sustained drop in blood pressure noted in conjunction with the administration of prostigmine and

charge directly antagonizes the negative charge set up by acetylcholine, hence the rationale for the use of phenobarbital and dilantin in the treatment of epilepsy. The view that excess acetylcholine with resultant increased negativity and stimulation plays a part in the etiology of epilepsy has long been held by these investigators.

\* It has been shown experimentally by Barnes and Beutner<sup>2</sup> *in vitro* experiments that both phenobarbital and dilantin sodium give rise to positive currents in their oil cell experiments. This generation of a positive

sodium nitrite. This lowering of arterial pressure has persisted during her convalescence rising but slightly on resumption of activity.

#### COMMENT

Kabat<sup>6</sup> has reported encouraging results using neostigmine in various cases of neuromuscular dysfunction. Of particular interest are his results in cases of hemiplegia of cerebral vascular origin, monoplegia, and cerebral palsy. This observer reports a decrease in spasticity, increased range of passive motion, decreased deformity, relief from muscle pain and increase in voluntary motion in his cases of hemiplegia. Improvement was noted in his cases of monoplegia and definite improvement of spasticity and some improvement in strength and coordination in the cases of cerebral palsy in which prostigmine was employed.

Kabat recommends the subcutaneous injection once or twice daily of 2 cc. of neostigmine methyl sulfate 1-2000 solution plus  $\frac{1}{100}$  gr. to  $\frac{1}{150}$  gr. of atropine sulfate.

One of us (J. C. D.) has recently successfully employed prostigmine bromide in oral doses of 15 to 30 mg. three times a day for the relief of spasticity in multiple sclerosis, and of postoperative hemiplegia in a patient with a pituitary gland tumor.

Jepson<sup>5</sup> treated twenty-five cases of infantile cerebral paralysis using oral prostigmine bromide in doses of 5 mg. three times a day. The medication was continued for at least six months or as long as improvement was noted. The chief results achieved in this series seemed to be a decrease in muscle spasm and an increase in function of the muscles involved.

The results noted in the references cited above are similar to the results noted in the case presented. The rapid rate of recovery seen in this patient coincided with the period during which prostigmine was administered.

Whether the drug brings about its therapeutic effect through relief of spasticity,

as in treatment of arthritis and poliomyelitis, or whether actual aid in healing the central nervous system lesions is brought about, is not known. Ward and Kennard<sup>9</sup> present evidence that actual aid in healing results following the use of prostigmine. Doryl, a cholinergic drug, was used in their experiments to treat lesions of the central nervous system in monkeys, and here accelerated recovery of function was reported. Prostigmine 0.01 per cent has been used by Welsh<sup>10</sup> to aid in the regeneration of a cut planarian. He maintains that acetylcholine, a physiologic cholinergic agent, is a trophic substance maintaining the integrity of neurones and hence should aid in healing. Whether prostigmine acts by neutralizing choline esterase and thus allows excess acetylcholine to accumulate and achieve a therapeutic effect, or whether it has an independent cholinergic action of its own is as yet unknown. Evidence at hand seems to suggest that the latter supposition is correct.

Niker<sup>8</sup> et al. believe that prostigmine produces cholinergic effects of its own. After blocking choline esterase effects with a suitable physiological agent, they noted that muscular contractions could be elicited with prostigmine.

Eserine, a cholinergic drug which supposedly produces its effect solely by neutralization of choline esterase with subsequent increase in acetylcholine, has been shown to have less physiological effect than prostigmine both *in vitro* and *in vivo* experiments. Williams<sup>11</sup> reports that intravenous administration of prostigmine in much smaller amounts than eserine increased petit mal brain waves in epileptics. Barnes<sup>2</sup> found that the electrical potential set up by prostigmine in oil cell experiments is much more lasting than that caused by eserine. He states that the electrical effects of prostigmine are the factors important in nerve cell regeneration and that the action

currents thus set up aid in bridging neural connections.

Of note also in this case is the reduction in blood pressure coincident with the administration of the drug. Although prostigmine has been reported to have some peripheral vasoconstricting action by Mendez and Ravin,<sup>7</sup> still as a cholinergic drug the peripheral action should be primarily one of vasodilation. If the cholinergic action of prostigmine as a vasodilator is of use, as suggested by this case, in bringing about the lowering of blood pressure in selected cases of essential hypertension, then rich avenues of investigation are opened in view of the theories generally held that essential hypertension is of neurogenic origin.<sup>4</sup> Its main action, however, may be only the prevention of the overstimulation of sympathetic fibers, the antagonistic action of cholinergic and adrenergic drugs and their effects on peripheral vascular structures being an accepted physiological fact. This possible relationship of prostigmine therapy to the drop in blood pressure must as yet of necessity be limited to the sphere of theoretical speculation.

#### SUMMARY

A report of a patient with hemiplegia probably due to cerebral hemorrhage is presented. It seemed that excellent therapeutic results were obtained by using prostigmine bromide orally. Rapid return

of strength, an increase in range of motion, and decreased spasticity, as well as a greatly improved general condition, were manifested promptly. The therapeutic results far surpassed the prognostic hopes held for the patient.

Reports of other patients thus treated and a brief discussion of theoretical implications involved are presented.

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## Rutin

ONE of the greatest difficulties in the evaluation of a new drug or biological product is securing proper control observations. This is especially so in the case of chronic disease which runs a variable and uncertain course such as hypertension or chronic hepatitis, or with disorders in which the complaints are mainly subjective, for example, migraine. What one needs, of course, are objective criteria of drug action, capable of measurement, and in the end, of statistical analysis.

The use of methionine in chronic hepatitis (cirrhosis) is a case in point. There is ample objective evidence that methionine has real protective and curative influence in certain types of experimental liver damage; in the human, on the other hand, it is difficult to secure convincing effects which have not been duplicated in other patients observed before the modern treatment of cirrhosis was introduced. Migraine illustrates the same problem. Here benefit or even cure has been claimed with every conceivable agent; and at the present time good results seem to be obtained by some with infusions of histamine, when at the same time other observers prefer to treat certain types of headache with so-called anti-histaminic drugs. The truth of the matter probably is that suggestion, chance, faith and intangible variables enter so much into the situation with these vague and ill defined conditions that really conclusive evaluation of therapeutic agents is almost impossible. It behooves the clinical investigator, therefore, to make every effort to select patients in whom the results of therapy can be gauged accurately.

Rutin, a new agent, for which certain

therapeutic claims have been made with reference to disturbances of capillary fragility and permeability, presents similar problems. Rutin is said to be a glucoside of quercetin which can be obtained from various leafy plants and flowers. Buckwheat leaves have been the source of some of the available material. It is a flavone derivative related to those substances found in "citrin," an extract of lemon, which under the designation vitamin "P" has already been studied for its effects on capillary permeability, with dubious or certainly controversial results. The question has been raised as to whether rutin is the active substance in citrin. Just how rutin is supposed to act is not clear. When we recall that capillary permeability and so-called "fragility" may be altered either by disorders of the capillary membrane itself or on the other hand by changes in the cement substance between the endothelial cells, and when we realize that the cement substance in turn is affected by all sorts of variations in reaction and in concentration of various blood ions, it becomes clear how complicated the situation is and how difficult a really critical evaluation of any substance from the standpoint of its effect on "capillary fragility" must be. To call rutin vitamin "P" or give it such a general designation as the capillary permeability regulating vitamin hardly seems justifiable as yet.

Meanwhile, as pointed out recently,<sup>1</sup> reports have become prevalent that rutin is of value in the treatment of hypertension although it appears that no such claims

<sup>1</sup> Report of the Council on Pharmacy and Chemistry. *Rutin*. *J. A. M. A.*, 131: 743, 1946.



have actually been made in the published literature. It has been found, however, that the use of rutin may be followed by lessening of capillary permeability under certain conditions as measured by a standard petechiometer test.<sup>2</sup> Since the material seems to produce no toxic effects in man and is furnished in the form of small, practically tasteless pellets which can be taken simply by mouth, a thorough appraisal in clinical conditions in which capillary fragility is altered seems worth while. As far as hypertension is concerned, those seriously ill patients who have marked changes in the smaller vessels, especially in the eye grounds, with hemorrhage and

<sup>2</sup> SHARMO, R. L. Rutin: a new drug for the treatment of capillary fragility. *Am. J. M. Sc.*, 211: 339, 1946.

edema certainly deserve the benefit of a trial with a harmless agent of this sort in the face of a prognosis which otherwise is absolutely bad. It is to be hoped, however, that those working with the material will select cases capable of evaluation and will make objective observations with meticulous care in order to learn as soon as possible what rutin really accomplishes.

There would also seem to be an interesting field in the laboratory for studies of the effect of rutin on experimental capillary damage in the light of modern knowledge of the pathological physiology of the minute vessels. It should be easy to devise experiments which would be decisive, especially if beneficial results were obtained.

A. L. B.

## Streptomycin Treatment of Urinary Tract Infections\*

*With Special Reference to the Use of Alkali*

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THERE are a number of reports on the streptomycin treatment of urinary tract infections caused by susceptible gram-negative organisms.<sup>1-9</sup> The clinical results have been quite variable. Some authors have advocated alkalization of the urine during streptomycin therapy,<sup>8,10,11</sup> but to date there have been no convincing data to indicate that the clinical results of streptomycin therapy are favorably influenced by alkalization of the urine. The purpose of this report is to present clinical and bacteriological observations in twenty-one streptomycin-treated patients with urinary tract infections, of whom fourteen were also treated with alkalis.

### CASES, MATERIALS AND METHODS

*Case Selection.* Adult patients with urinary tract infections were selected for streptomycin treatment because other forms of therapy either had failed or seemed undesirable for them. The organisms isolated from cultures of the urine were proved first to be susceptible to the action of streptomycin, *in vitro* and, in most cases, to be inhibited by the concentration of the antibiotic expected in the blood and urine. One or more

courses of sulfonamide drugs had been given to sixteen patients prior to streptomycin treatment and the infection persisted in eleven of these cases in spite of an adequate course of the sulfonamides. In the remaining five patients, sulfadiazine therapy was started, but was soon discontinued either because of sensitivity reactions (two cases) or because of poor excretion of the drug (three cases). Sulfonamides were withheld from three patients who had hypertensive cardiovascular disease and from one who had congestive heart failure. Penicillin had been given to ten patients, methenamine to four and mandelic acid to one, without response in each instance.

The approximate duration of infection was known in seventeen cases: ten had infection of a year's duration or longer, two had had urinary symptoms for a period of between six and twelve months. In four patients the onset of symptoms was about two months before the streptomycin treatment and one patient had an infection of only two weeks' duration that proved unresponsive to both sulfadiazine and penicillin. The remaining four patients had chronic infections, the duration of which could not be determined. Retrograde pyelograms had been done in eleven of the patients and anatomical abnor-

\* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Mallory Institute of Pathology, Boston City Hospital and the Department of Medicine, Harvard Medical School. The streptomycin was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents. These studies were aided, in part, by a grant from the United States Public Health Service.

malities were demonstrated in ten of them. Dilated pelves or ureters were found in five cases, slight dilatation of the minor calyces in one and renal stones in three. One patient had a spina bifida and loss of sphincter control and cystoscopy in that case showed a dilated bladder and a urethral diverticulum containing a stone. Diminished renal function was found in seven patients. In three of these patients it was probably the result of the infection while in the other four it was associated with hypertensive cardiovascular disease. The remaining patients showed no functional renal abnormality.

*Bacteriological Studies.* Cultures of the urine were made in liquid media and on the surface of solid media before, during and after the streptomycin treatment. Agar pour plates of 10-fold dilutions of the urine were also made in most cases in order to quantitate the numbers of bacteria present. Blood cultures were done in almost every case but only those in Case 15 were positive. All of the different strains of bacteria encountered were isolated in pure culture on streptomycin-free media and then preserved in the frozen state so that the morphological, cultural and biochemical characteristics of the organisms isolated at different times from the same patient could later be compared under nearly identical conditions.\*

*Sensitivity of the Strains.*† Tests for sensitivity were carried out with cultures derived from single colonies of the organisms grown in brain heart infusion broth (Difco), pH 7.4, and the same medium was used for diluting both the organisms and the streptomycin. Equal volumes of a  $10^{-4}$  dilution of culture containing approximately 100,000 organisms were added to serial 2-fold dilutions of streptomycin and incubated for twenty-four hours. Tubes in which there was no visible growth were then subcultured to streptomycin-free nutrient agar and incubated for twenty-four hours longer. The sensitivity was considered to be the minimum concentration of

streptomycin (M.I.C.) in which there was no growth in the broth and on the agar. The broth used for the inoculum also contained 1 per cent defibrinated horse blood which served as an indicator of growth. Control observations showed that this amount of blood neither stimulated growth of the standard strain nor inhibited streptomycin action in this medium. A type A Friedländer's bacillus, strain T, used as a standard in this laboratory was always included as a control. This organism is inhibited by 0.78 units but not by 0.39 units of streptomycin.

*Streptomycin Levels.* The concentrations of the streptomycin in blood and urine were determined by a dilution method similar to that used in the tests of sensitivity. Strain T was used as the test organism; the inoculum was  $10^{-4}$  cc. containing 50,000–100,000 organisms, and 2-fold dilutions of the urine and plasma were made in broth.

*Treatment.* Almost all of the streptomycin was given intramuscularly. The total daily dose was 2.5 to 6 Gm. given in 0.5 to 1.0 Gm. amounts every four to six hours. The numbers of patients receiving the different daily doses were as follows:

Gm. per Day	No. of Cases
2.5	1
2-3	2
3.6	1
4.0	9
4.8	3
5.4	2
6.0	3

An initial intravenous dose of 0.5 to 1.0 Gm. of streptomycin was given to nineteen of the patients immediately before the first intramuscular injection. The intravenous doses were given in a volume of 20 ml. and the intramuscular doses in 4 or 5 ml. of physiological sodium chloride solution. The streptomycin treatment was usually continued for about seven days unless an untoward reaction prompted its discontinuance. One patient, whose urine contained *Streptococcus viridans* as well as a gram-negative organism, was given intramuscular penicillin 320,000 units daily along with the streptomycin.

The urine was alkalinized before and during treatment in fourteen cases. This was done by the oral administration of sodium bicarbonate

\* These studies were carried out, in large part, in the bacteriological laboratory of the Mallory Institute of Pathology with the help and guidance of Miss Marion E. Lamb and Dr. Robert N. Nye who were also helpful in the classification of the organisms.

† These determinations and the streptomycin levels were done by Clare Wilcox.

and potassium citrate, the usual dose being 1 Gm. of each six times daily. Slightly higher doses were necessary in four cases in order to keep the urine alkaline. Two patients received only sodium bicarbonate. Generally, the patients were kept on the alkali therapy for a control period of at least two days before streptomycin was begun, in order that the effect on the urinary flora could be ascertained. However, only one case included in this study showed a significant reduction in the bacilluria by alkalization alone.\* In seven patients, six of whom are included in a previous report<sup>7</sup> no attempt was made to alter the urinary pH.

#### CASE REPORTS

The patients in the first six cases were treated with streptomycin without adjuvant alkali administration. The pyuria and bacilluria were unaffected and *in vitro* tests showed that the failures were associated with the rapid development of streptomycin resistance by the infecting organisms. These six cases are reported in detail elsewhere.<sup>7</sup> The urine was acid before and throughout the course of therapy in five of these six patients.† In Case 6, the specimens of urine obtained immediately before streptomycin treatment was started were alkaline. Only *B. proteus* could be isolated from cultures of these specimens and from the ones obtained during the first two days of therapy although the urine became acid immediately after the streptomycin was started and remained acid throughout the period of observation. No organisms could be grown from the cultures of the urine obtained on the third and fourth day of treatment in this case but pyuria and bacilluria recurred on the fifth day of therapy. The organism recovered on that day and thereafter was a strain of *E. coli* that was totally resistant to streptomycin. Earlier cultures in this case were reported as showing both *B. proteus* and *E. coli* but the latter organism could not be isolated from cultures obtained during the three-day

control period just prior to the streptomycin administration.

In only one patient treated without alkalis did the urinary tract infection respond favorably to streptomycin.

CASE 7. The significant data in this case are shown in Figure 1. The patient had rheumatic heart disease and had many hospital admissions for attacks of congestive cardiac failure, pulmonary emboli and paroxysmal tachycardia. Since 1940 she also had marked but symptomless pyuria which failed to respond to the usual therapies, including several courses of sulfonamides. In May, 1946, she was admitted because of severe dyspnea, some edema and moderate precordial pain. At that time left costovertebral angle tenderness was elicited but there was no suprapubic discomfort. Repeated urine examinations showed gross pyuria, 3+ albumin, and numerous gram-negative bacilli. Cultures of the urine all showed *Escherichia coli*. The cardiac symptoms responded promptly to rest and digitalis. On the sixth day in the hospital she was started on streptomycin. Alkalis were not given but the ammonium chloride which she had been receiving was discontinued during the streptomycin therapy. The blood nonprotein nitrogen was 34 before and 25 mg. per 100 cc. after this therapy. Although the urine remained markedly acid, the coli bacilluria and the pyuria cleared rapidly and did not recur during a four-month follow-up except for a few leukocytes seen in the sediment on one occasion.

There were five patients (Cases 8–12) from whose urine a single organism was cultured and who responded favorably to streptomycin and alkali therapy. The infecting organism was *Aerobacter aerogenes* in three of them and *Escherichia coli* in the other two. Except on two occasions shortly after the end of treatment in Case 10, the urine remained sterile in every instance during the therapy and over a follow-up period varying from seven weeks to five and one-half months. The pyuria cleared completely in three of these cases and was markedly diminished but persisted in the other two so that only a few pus cells were seen on microscopic examination of the spun sediment of urine collected after the first two or three days of streptomycin. The relevant information concerning these cases is

\* There were two patients, however, in whom the infection cleared during the control period when alkalis were given alone. Streptomycin was not used in these cases and they are not included in this report.

† In the present report the cases are numbered consecutively and Nos 1–6 correspond to those previously reported.<sup>7</sup>

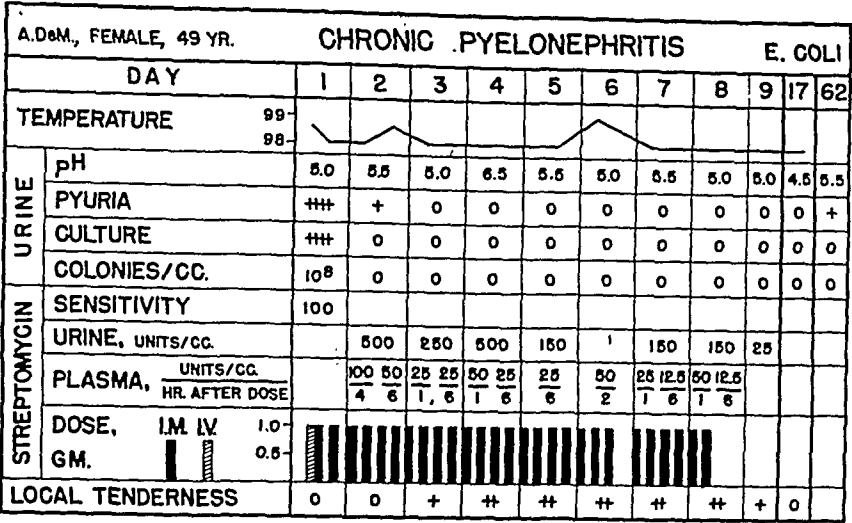


FIG. 1. Case 7. Alkalis were withheld in this case because of congestive heart failure. The streptomycin treatment was successful although the urine remained acid throughout.

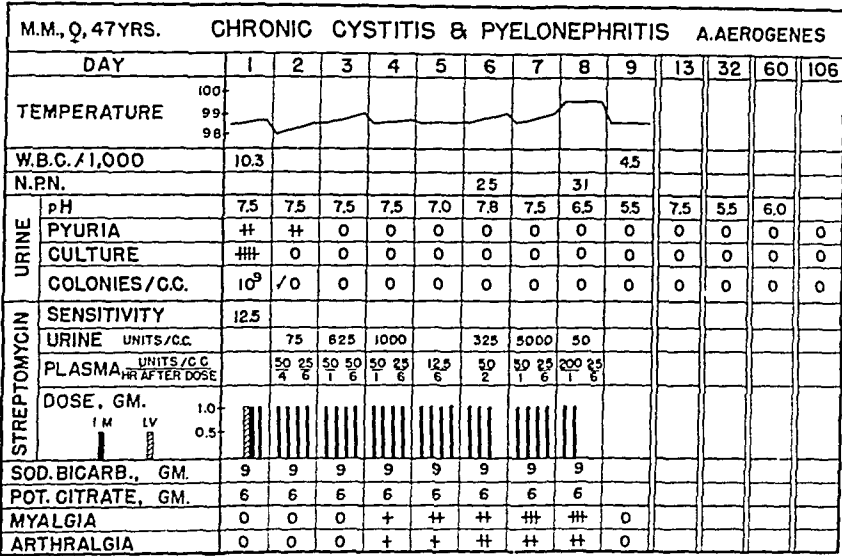


FIG. 2. Case 8. The patient entered the hospital in diabetic coma from which she recovered on appropriate treatment. In the meantime, she developed cystitis and pyelonephritis presumably through a catheter which had been kept in place for several days. Three separate courses of sulfadiazine and one of sulfathiazole failed to control the pyuria and the bacilluria. The infection had been present for three months when therapy with alkalis and streptomycin was begun. At that time the patient was convalescing from acute infectious hepatitis of about a month's duration. The urinary infection responded promptly and the urine has remained sterile and free of pus during a three months' follow-up. Albumin was found in the urine before but not after the treatment. Renal function was normal throughout and liver function improved steadily. Arthralgia and myalgia occurred and increased in severity during the latter part of the therapy and fever appeared on the last day, but all these manifestations cleared promptly after streptomycin was stopped.

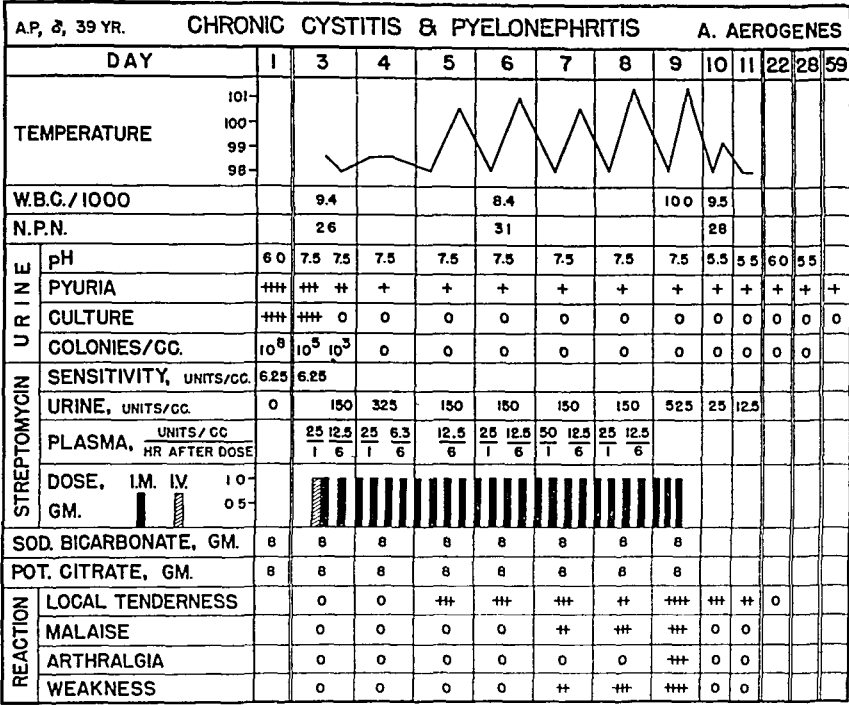


FIG. 3. Case 9. This patient underwent a surgical resection of the rectum for carcinoma and developed cystitis and pyelonephritis from an indwelling catheter. During three months of persistent infection, separate courses of sulfadiazine, sulfathiazole and penicillin were given without effect. Urinary alkalization and streptomycin treatment resulted in rapid clearing of the bacilluria but a few pus cells were seen in the sediment of the later specimens. There was no alteration in renal function in this case. The patient has had no symptoms and urine cultures have remained sterile during a follow-up period of seven weeks. Fever, malaise and arthralgia cleared promptly after the streptomycin was discontinued but the gluteal tenderness subsided more slowly.

given in Figures 2-6 and in the legends which accompany these figures.

There were three other cases (Cases 13-15) in which a single organism was isolated before treatment but only temporary improvement was obtained by therapy. In each instance an organism was isolated after treatment which was different from the one found during the control period before streptomycin was started. In one case an organism resembling the original strain also appeared at a later date. With one exception the new strains isolated after treatment were sensitive to streptomycin.

The findings in Case 13 are shown in Figure 7. The late recurrence of pyuria and bacilluria during the sixth week after the treatment was stopped was considered to be a reinfection in this case. The significance of the dizziness and instability that were noted after the therapy was

difficult to evaluate in view of the previous history of the patient.

In Case 14, there was only slight and temporary improvement but a streptomycin resistant strain of *Aerobacter aerogenes* replaced the original sensitive strain of *E. coli* in the urine. The possibility that the *Aerobacter* was present but undetected in the urine before treatment cannot be ruled out. The findings are shown in Figure 8.

In Case 15 (Fig. 9) there was temporary improvement with a recurrence of infection, first with a new strain not previously isolated and later with an organism similar to the original strain in every respect including its sensitivity to streptomycin. The new strain also was sensitive to the antibiotic.

The next three cases (Cases 16-18) are of interest because in each instance the urine was

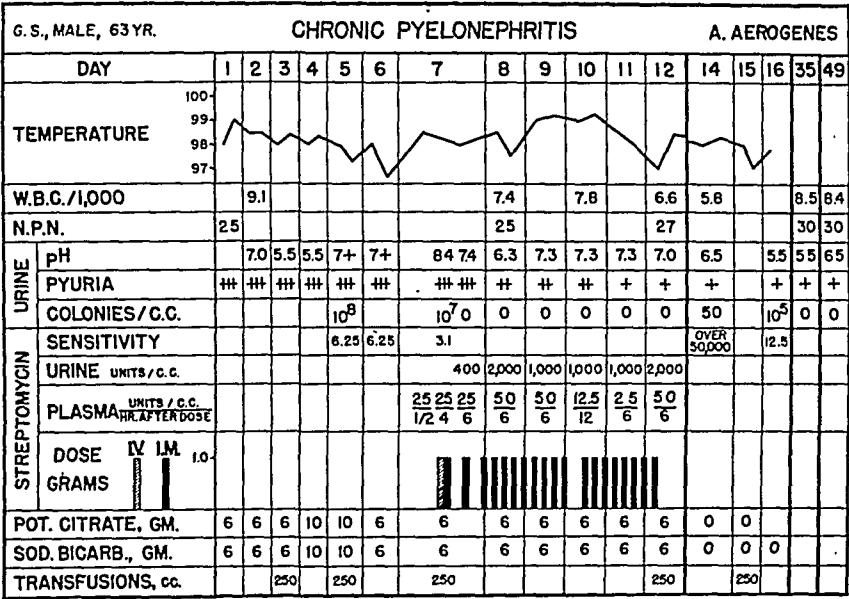


FIG. 4. Case 10. The urinary tract infection followed suprapubic removal of a papillary carcinoma of the bladder. Cystoscopy revealed no recurrence of the tumor but retrograde pyelograms showed dilation of the right ureter and renal pelvis. There was no diminution of renal function. A course of sulfadiazine had been unsuccessful and pyuria and bacilluria with *Aerobacter aerogenes* had been present for ten weeks before urinary alkalinization and streptomycin therapy was begun. Cultures were negative during treatment, but *A. aerogenes*, which grew in the presence of 50,000 units of streptomycin per cubic milliliter, was obtained on the second day after the treatment was ended. Two days later, at the time of discharge from the hospital, a streptomycin sensitive strain of the same organism was recovered. Except for these two occasions the urine was sterile and remained so during a follow-up period of five and one-half months. Microscopic pyuria, however, has persisted. No other treatment was used for the urinary infection. Local tenderness at the sites of the injection was the only untoward effect of the streptomycin.

infected with two organisms and the infection responded to alkalinization and streptomycin. Two of these cases had renal calculi and in the third the urinary infection was secondary to an acute prostatitis.

CASE 16. This was the patient's sixth hospital admission. In 1943, he had hematuria and lumbar pain for two months and was then found to have bilateral staghorn calculi. A right pyelolithotomy was performed in July of that year and a left nephrectomy, three months later. In November, 1943, the patient developed acute pyelonephritis, was treated with sulfathiazole and made an uneventful recovery. In March, 1945, he had a second attack of acute pyelonephritis. At this time *B. proteus* and Friedländer's bacillus were obtained from cultures of the urine. Sulfadiazine therapy was begun

but had to be discontinued because of high drug levels in the blood. Methenamine therapy was instituted and the patient became symptom free but the pyuria persisted. In February, 1946, he had a third attack of pyelonephritis. Treatment with sulfadiazine, penicillin and methenamine was followed by symptomatic improvement but the pyuria and bacilluria were unaffected. An intravenous pyelogram then revealed two small stones in the right kidney.

The patient was admitted for streptomycin therapy on May 6, 1946. He was then symptom free and afebrile. His blood pressure was 150/100. Mild tenderness was elicited in the right upper quadrant of the abdomen. Routine hematological findings were normal. The urine was cloudy, malodorous, showed 2+ albumin and the centrifuged sediment contained in-


J.G., FEMALE, 65 YR.		CHRONIC PYELONEPHRITIS							E. COLI		
DAY		1	2	3	4	5	6	8	12	19	
TEMPERATURE	99										
	98										
W.B.C. / 1000		6.4		7.2	6.8			54			
N.P.N.		37			47			44			
URINE	PH	8.0	8.0	7.5	8.3	7.8	8.0	5.2	5.0	5.0	
	PYURIA	+++		+++	+++	+	+	+	0	0	
	CULTURE	+	0	0	0	0	0	0	0	0	
STREPTOMYCIN	SENSITIVITY	12.5									
	URINE UNITS / C.C.	0	312	625	625	1250	78				
	PLASMA <small>UMITS / C.C. HR. AFTER DOSE</small>	0 / 0	25 / 1   25 / 4	25 / 4	100 / 4	25 / 4	31 / 24				
	DOSE <small>IV. IM.</small> GRAMS										
SOD. BICARB., GM.		6	6	6	6	6	0	0	0	0	
POT. CITRATE, GM.		6	6	6	6	6	0	0	0	0	

FIG. 5. Case 11. This patient was admitted for acute gastroenteritis, but was found to have persistent pyuria and bacilluria, and *E. coli* was cultured from the urine. Culture of the urine became negative promptly after alkali and streptomycin therapy was started. The urine became grossly clear on the third day and the sediment was free of pus cells within a week. Treatment was concluded on the fourth day because of moderate vertigo which began on the second day but this disappeared one day after the streptomycin was stopped. Many subsequent urine cultures have been sterile and only an occasional pus cell has been found in the spun sediment of some of the specimens obtained during a three months' follow-up.

numerable pus cells and bacilli and a few red blood cells and fine granular casts. Cultures of the urine all yielded an "atypical" Friedländer's bacillus and *B. proteus*. There was poor excretion of dye and the maximum concentration of the urine was low. Chloride, calcium, phosphorus and phosphatase determinations in the blood were normal. Therapy with sodium bicarbonate was begun eight days after admission and streptomycin was started three days later. The relevant findings thereafter are shown in Figure 10. The first urine culture obtained seventeen hours after the initial dose was sterile. Numerous additional cultures made during treatment and during the three-month follow-up period were all sterile. Pyuria, however, was only temporarily reduced during the last three days of treatment. The blood non-protein nitrogen was somewhat elevated but was unaffected by the treatment.

Local tenderness developed in the injection sites on the third day and increased progressively with each injection. On the ninth and tenth days the gluteal regions showed large areas of redness, heat and induration. At this time a reddish maculopapular rash appeared on the extensor surfaces of both thighs and on the back. After the second day of treatment, the patient complained of mild dizziness while walking but the neurological examination was negative. Streptomycin was continued and the vertigo cleared for three days and then reappeared along with some headache on the eighth day. These symptoms increased during the next two days and on the tenth day there was marked headache, tinnitus and vertigo, the latter occurring with any motion of the head. The patient was unable to walk because of unsteadiness. Treatment was then omitted. The symptoms disappeared within six hours and the



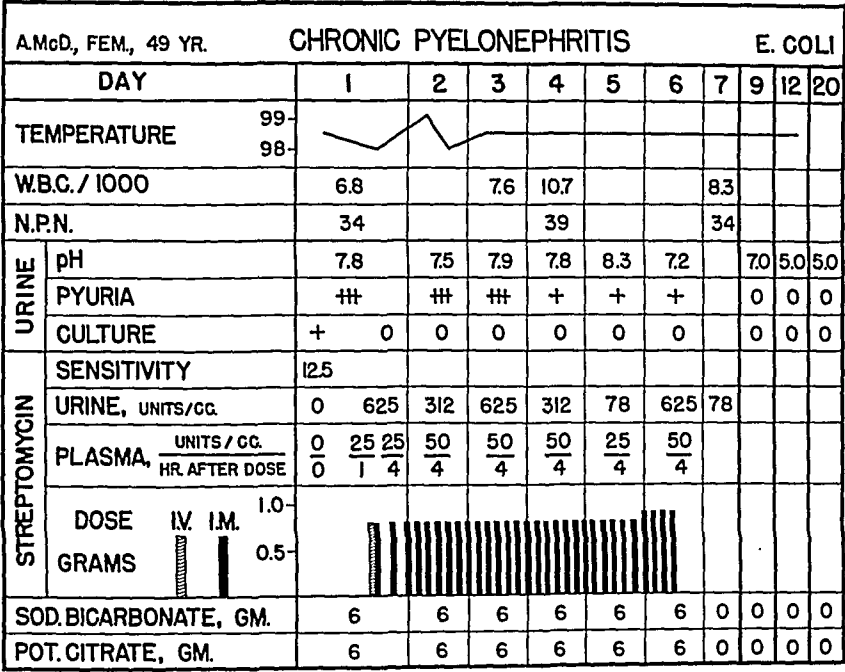


FIG. 6. Case 12. The patient had hypertension (blood pressure 240/130) and slightly diminished renal function (dye excretion and concentration of the urine) but no urinary tract symptoms except nocturia. She was admitted to the hospital because of urticaria which followed medication with penicillin and other drugs that were given at another hospital for an acute gastrointestinal upset. The urticaria and symptoms cleared promptly but she was found to have persistent pyuria and bacilluria without albuminuria. After alkalinization of the urine, streptomycin was given. The urine promptly became sterile and remained so for a follow-up period of two months. The urine remained cloudy for two days, then showed only a few pus cells in the sediment for three more days and finally cleared completely and has remained clear. There were no untoward reactions during the treatment, but eight days after it ended the patient developed ataxia. Caloric and rotation tests showed reduced labyrinthine function but there was no vertigo, tinnitus or nystagmus. The ataxia improved within a month and the patient walked normally after two months.

patient remained symptom-free for five days. Severe vertigo and mild tinnitus then recurred. A neurological consultant found no neurological changes other than marked subjective discomfort on sudden motion of the head and unsteadiness of gait and considered this to be an acute labyrinthine disturbance. Caloric and irrigation tests were negative and audiograms were essentially normal. Five days after the second attack of vertigo began, the patient became ambulatory but his gait continued to be unsteady. One month later he observed motion of distant objects in the lateral fields of vision and examination revealed slight but sustained nystagmus on extreme left lateral gaze. The nystagmus and vertigo gradually subsided

during the next month, but the unsteady gait persisted.

CASE 17. This patient had had three attacks of acute left pyelonephritis at three-month intervals before January, 1946, when he was found to have bilateral renal calculi. A right pyelolithotomy was performed at that time and he was given sulfadiazine, 4 Gm. daily for two months but the pyuria persisted. In June, 1946, he was treated with methenamine. Again his symptoms improved but the pyuria was unaffected. His blood pressure and renal function tests were normal. Retrograde pyelograms showed calculi in the pelvis of the left kidney. Cultures of the urine from the right ureter grew Friedländer's bacillus and those from the left

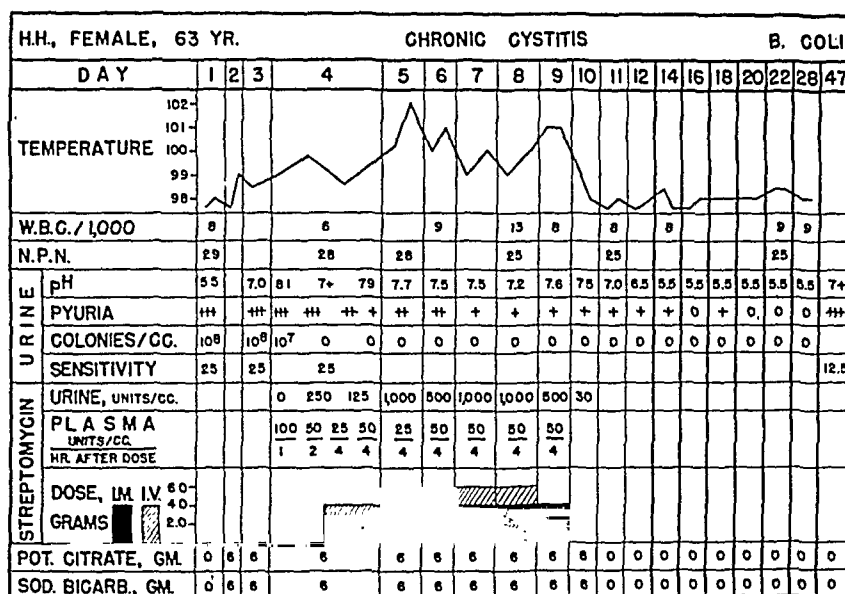


Fig. 7. Case 13. This patient had recurrent attacks of cystitis for many years, and weakness, dizziness and anorexia for four months. Marked pyuria and bacilluria were demonstrated during the ten days prior to streptomycin treatment. The blood pressure was 180/100 but the renal function was normal. The urine was rapidly sterilized after alkalinization and streptomycin administration and remained free of bacteria until the patient was discharged nineteen days later. During the sixth week after the treatment ended, the urinary infection recurred. The organism at this time, however, was a strain of *B. coli communis*, sensitive to 12.5 units, whereas the organism isolated on two occasions before treatment was *B. acidilactici*, sensitive to 25 units of streptomycin. As the patient became ambulatory, she complained of dizziness and had difficulty in walking for about five days, and the dizziness persisted in a minor degree throughout the follow-up period. There were no abnormal neurological findings.

yielded the same organism and also *B. fecalis alkaligenes*. Both of these organisms were found in numerous cultures of bladder urine.

Therapy with alkalis and streptomycin was started early in July. The relevant findings are shown in Figure 11. Cultures of urine obtained one and two hours after the first dose of streptomycin each showed a scant growth of Friedländer's bacillus. Those obtained thereafter, both during treatment and during a followup period of six weeks, were all sterile except for the appearance of *Pseudomonas aeruginosa*, probably as a contaminant, on one occasion. The pyuria decreased initially but recurred during the last three days of therapy and persisted thereafter.

CASE 18. A twenty-three-year old man entered the hospital twenty-four hours after the onset of chills, fever, nausea, vomiting and dysuria. On admission his temperature was 100°F. and pulse 100. There was tenderness in

the suprapubic region, in both costovertebral angles and over the prostate. The urine was alkaline, contained a trace of albumin, and an occasional pus cell in the centrifuged sediment. Cultures yielded *Staphylococcus albus* and *Pseudomonas aeruginosa*. During six days of treatment with penicillin and sulfadiazine, the temperature returned to normal and the symptoms cleared but the pyuria persisted and urine cultures continued to be positive. At this time the prostate was enlarged and tender. The strain of *Ps. aeruginosa* isolated from the urine was sensitive to 25 units of streptomycin and the *Staphylococcus albus* was inhibited by 50 units. Treatment with sodium bicarbonate, 10 Gm. daily, was begun on the tenth hospital day. The pH of the urine was 7.5 on the twelfth day and streptomycin was then started. The initial dose was 1 Gm. intravenously and 1 Gm. intramuscularly and this was followed by 1 Gm. intramuscularly

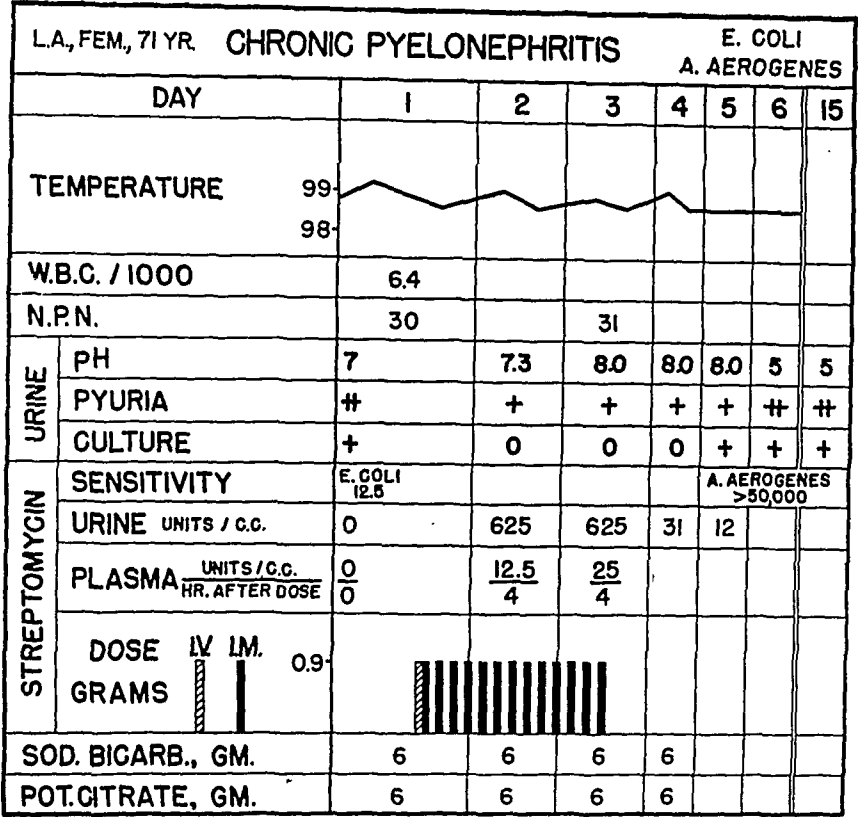


FIG. 8. Case 14. The patient was a mild diabetic who had had urgency, nocturia and occasional dysuria for one year and came to the hospital because of malaise, dysuria, frequency, fever and chills. With supportive therapy she quickly became asymptomatic but persistent pyuria was noted and *E. coli* was repeatedly cultured from the urine. The blood pressure was 180/96, there was a slight trace of albumin in the urine and the renal function was slightly diminished as judged by urine concentrations and dye excretion tests. Dizziness and some difficulty in walking were noted after forty-eight hours of therapy. The streptomycin was discontinued on that account and these symptoms subsided promptly. There was no tinnitus or nystagmus. Urine cultures were sterile during the first three days after institution of therapy, but on the fourth day and during a two-month follow-up period they all yielded a strain of *Aerobacter aerogenes* resistant to 50,000 units of streptomycin. The pyuria was diminished only temporarily.

every six hours for a total of 17 Gm. Tenderness at the injection sites was the only untoward reaction accompanying therapy. The pyuria and hematuria cleared and the urine cultures were sterile during treatment and thereafter. There has been no recurrence of symptoms, the urine has remained clear and cultures have been negative for three months.

The three remaining cases were all mixed infections which responded to treatment with alkalis and streptomycin by apparent temporary sterilization of the urine and by a reduction in the amount of pus. In each instance, however, the infection recurred, with

the same organisms in Case 19 and with different strains in Cases 20 and 21. The strains that reappeared in Case 19 had the same sensitivity to streptomycin as did the original strains, while the new strains that appeared in the others were of varying sensitivity.

CASE 19. This patient was first admitted to the hospital in April, 1946, because of acute prostatitis and pyelonephritis. *E. coli* and *B. proteus* were cultured repeatedly from the urine and from prostatic secretions. He was started on a course of sulfadiazine, 4 Gm. daily and became symptom free but some pyuria persisted. After five days, however, he developed



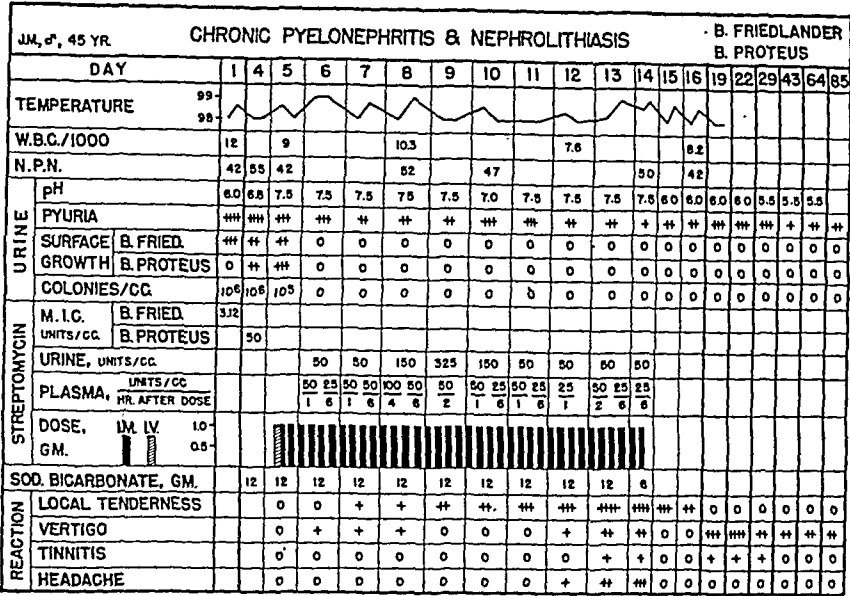


FIG. 10. Some of the relevant findings in Case 16.

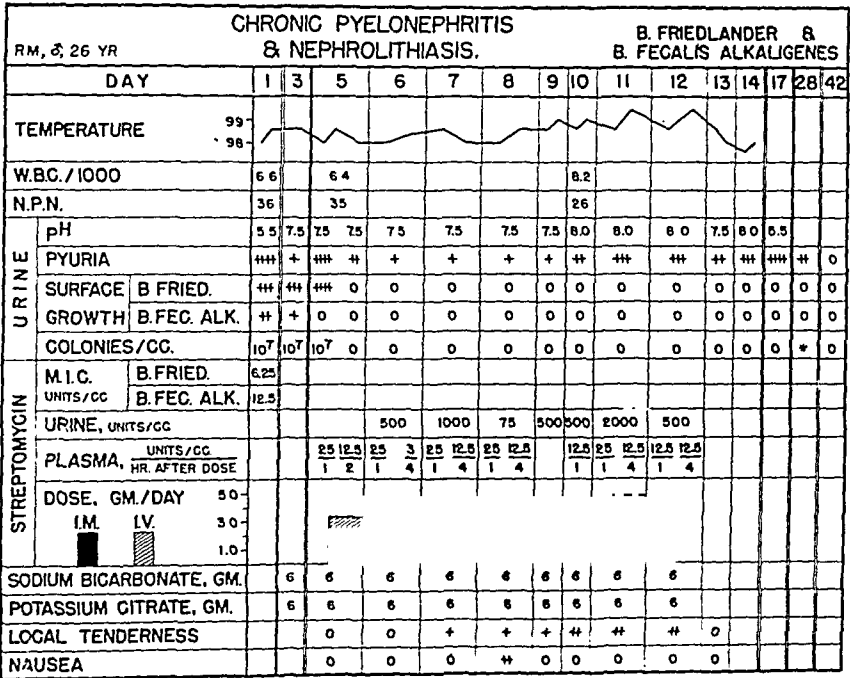


FIG. 11. Some data relevant to the streptomycin therapy in Case 17. *Pseudomonas aeruginosa* inhibited by 25 units of streptomycin isolated at this time only.

streptomycin was stopped. A culture of urine obtained one hour after the initial dose showed only a single colony of *E. coli* and one obtained after twelve hours was sterile. Pyuria cleared completely on the last day of therapy. The urine remained sterile throughout the streptomycin treatment and for a week longer. After that *E. coli* reappeared, and one week later, the urine was again purulent and contained both

*E. coli* and *B. proteus*. Pyuria and bacilluria have persisted during the month since they reappeared. The organisms obtained before and after the streptomycin had the same sensitivity to the antibiotic.

CASE 20. Sixteen months before entry this patient developed acute prostatitis which was treated successfully with penicillin. During the next five months he had three attacks of acute

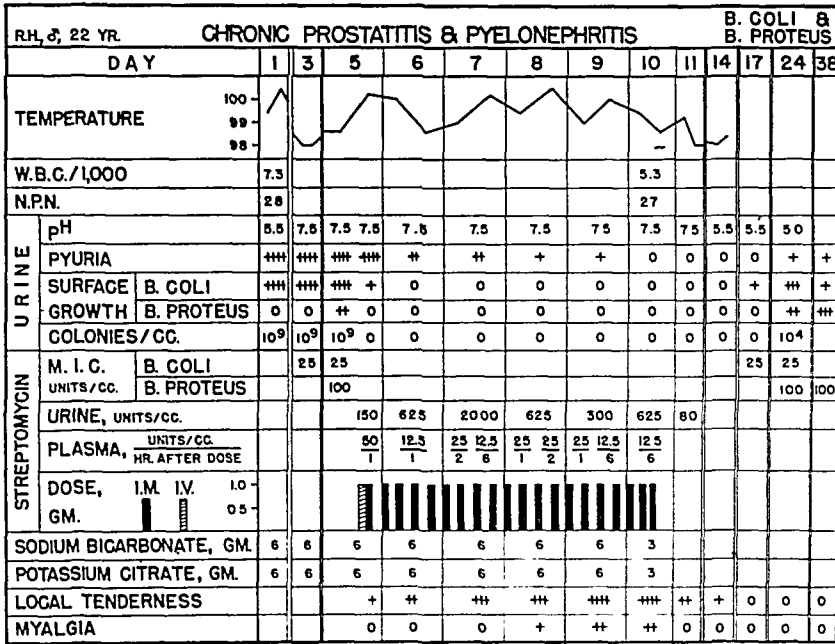


Fig. 12. Course and significant findings in Case 19.

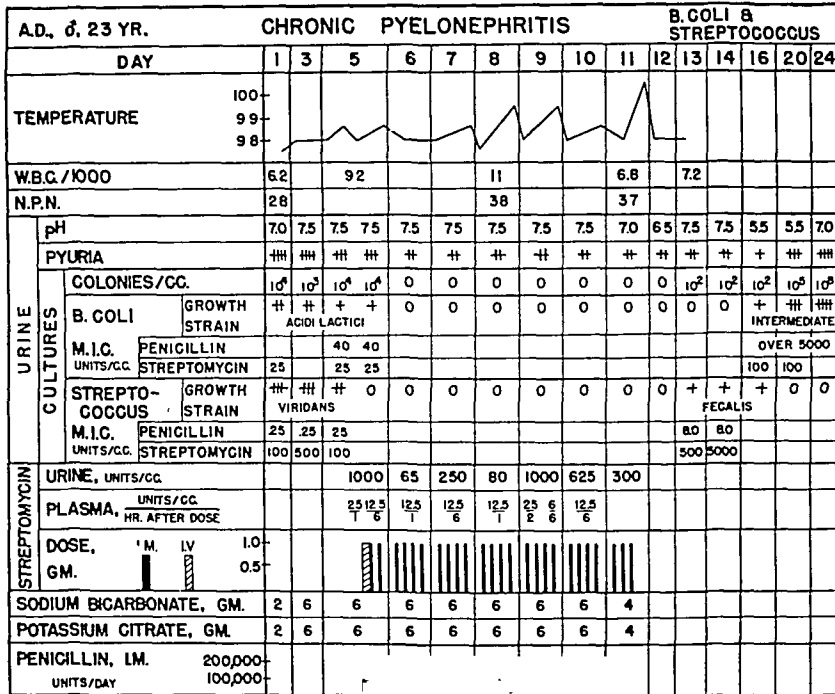


Fig. 13. Findings in Case 20.

pyelonephritis, the first one on the right, the others on both sides. The first and second attacks were treated successfully with sulfadiazine, but the development of neutropenia necessitated the omission of this drug during the third attack. Mandelic acid therapy was substituted and, although the symptoms regressed, pyuria and bacilluria continued for a period of eleven

months until he was admitted to the hospital in June, 1946. Five pyelographic studies during this interval showed no obstructive lesions and only minimal dilatation of the minor calyces. The renal function was normal and the urine remained free of albumin, casts and red blood cells. The patient was given alkalis and five days later was started on streptomycin. Penicil-

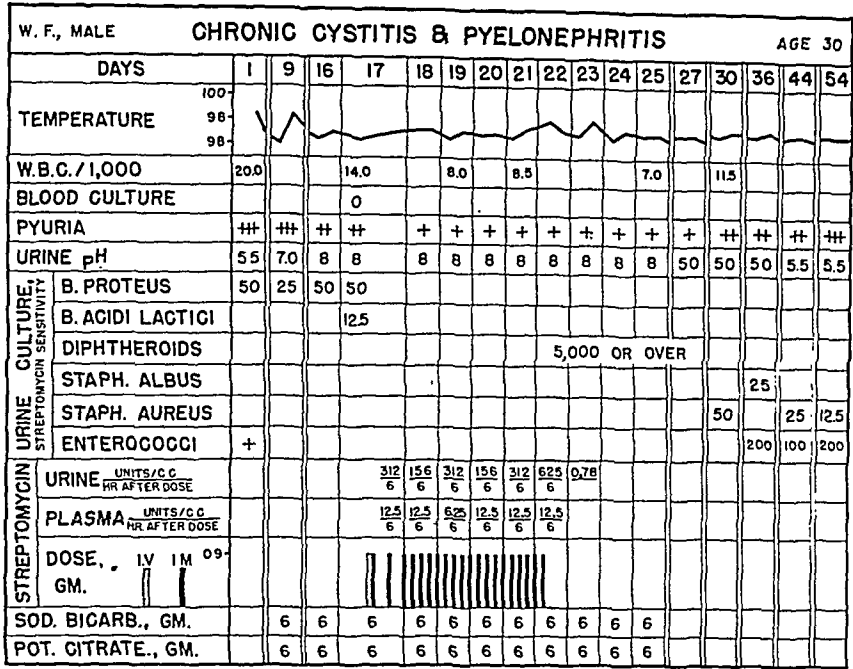


FIG. 14. Therapy and other significant findings in Case 21.

lin was given along with the streptomycin because the urine cultures showed both *Streptococcus viridans* and *E. coli* (acidi lactici type).

The therapy, course and other relevant data are shown in Figure 13. Tenderness and pain in the injection sites developed on the second day and persisted throughout the period of treatment and on the last day, there was also fever, headache, anorexia, malaise and generalized myalgia. These all disappeared within twenty-four hours after the streptomycin was discontinued. Urine cultures, one hour and six hours after the initial dose showed a scant growth of *B. coli*, but those obtained twenty-four hours later and throughout the period of therapy were sterile. The pyuria was considerably reduced throughout this period.

Two days after the streptomycin was discontinued an alpha hemolytic streptococcus appeared in the urine culture. This organism was different culturally from the one isolated before treatment and proved to be a strain of *Streptococcus fecalis*. It was also more resistant than the *Streptococcus viridans* to both streptomycin and penicillin. Three days later the urine culture yielded a coliform organism which was classified as the "intermediate type" of *E. coli* by its fermentation reactions. It was inhibited by 100 units of streptomycin but grew in the presence of 5,000 units of penicillin. Gross

pyuria and microscopic bacilluria have persisted and repeated cultures have been positive for *E. coli* during a two-month follow-up period.

CASE 21. The patient was a healthy looking, thirty-year old man who, on the day after his birth was operated on for a meningocele associated with spina bifida. He never had bladder control and used a Cunningham penile clamp for ten years. He had numerous episodes of cystitis and pyelonephritis and cultures of the urine at various times in the past had shown *B. proteus*, alpha hemolytic streptococci and enterococci. The patient entered the hospital this time because of dysuria, frequency and costovertebral angle pain of two weeks' duration having received a course of sulfadiazine without benefit just before entry. Blood pressure and renal function were normal. Pyelography and cystography revealed a large bladder and a dilated urethra with a diverticulum containing a stone. The kidney pelves and ureters appeared normal.

In the hospital, *B. proteus* was isolated repeatedly from the urine over a two-week period and *E. coli* (acidi lactici type) was also obtained just before a course of therapy with alkalis and streptomycin was given. The effect of the treatment on the pyuria and on the bacteriological findings are shown in Figure 14. A specimen of urine obtained four hours after

the first dose of streptomycin was negative as were daily cultures thereafter until the streptomycin was stopped. After that various gram-positive organisms were obtained of which only the enterococci had also been demonstrated before therapy. The gram-negative bacilli did not reappear during a follow-up period of four and one-half weeks. There was subjective improvement with disappearance of costo-vertebral angle pain and tenderness. These did not return during the period of observation. The number of pus cells in the urine diminished temporarily while the treatment was being given. The stone in the diverticulum was removed transurethrally before the patient left the hospital.

TABLE I  
RESULTS OF STREPTOMYCIN THERAPY IN RELATION TO  
ADJUVANT ALKALIS AND THE APPEARANCE OF  
RESISTANT STRAINS

Results of Treatment	Total Cases	Alkaline Urine	Acid Urine	Developed Resistance
Cured.....	9	8	1	1*
Transient improvement†.	6	6†	0	1
Failure.....	6	0	6	6

\* Patient received alkali. Resistant strain isolated only once after treatment and subsequent cultures were negative.

† One of these patients was free of infections for over five weeks and was considered as having a reinfection, since a different organism was found later.

#### RESPONSE TO TREATMENT

Sterilization of the urine was accomplished during streptomycin treatment in fifteen cases. In eight of them the urine was sterile within twelve hours after therapy began. The first negative cultures of the urine were obtained twelve to twenty-four hours after the initial dose had been administered to six patients, one patient showed persistence of bacilluria for forty-eight hours after therapy was instituted although there was a marked reduction in the number of bacteria found in the urine during this interval. Alkalis were used in the

treatment of all but one of these fifteen cases.

Of the seven patients who received streptomycin without urinary alkalization, five had persistent bacilluria throughout the period of therapy and only one of these five showed a significant reduction in the number of bacteria after therapy was instituted. In a sixth patient, cultures of the urine became sterile on the third day but there was a recurrence of bacilluria on the fifth day of treatment. Complete and lasting cure of bacilluria was accomplished in only one of these seven cases.

The pyuria was essentially unaffected in the patients from whom positive urine cultures were obtained throughout the period of treatment. In most of the other cases pyuria responded more slowly to therapy than did bacilluria. A significant reduction in the number of leukocytes in the urine occurred after one to four days of treatment in all of the fifteen cases whose urine cultures became negative. Complete disappearance of pus cells, however, occurred in only five of the cases. In two patients there was a reduction in the amount of pus in the urine during treatment but marked pyuria recurred after the streptomycin therapy was concluded, in spite of persistently negative cultures. Both of these patients had renal calculi. As would be expected, gross pyuria accompanied the relapses. Fever and symptoms referable to the urinary tract infection were quite mild in these cases and they responded irregularly to the therapy.

The results are summarized in Table I. "Cures" in the sense of freedom from bacilluria persisting throughout the period of observation were achieved in nine cases. Alkalis were used in eight of these cured cases. In another patient who was treated with alkalis, sterile urine cultures were obtained throughout the period of therapy and for five and one-half weeks after the



streptomycin was stopped but the urine subsequently became reinfected with an organism which had not been isolated before the streptomycin was started. Transient improvement with freedom from bacilluria during the streptomycin administration and for less than two weeks thereafter was noted in five additional cases, all treated with alkalis.

vidual cases are shown in some detail in the accompanying figures. The findings are summarized for the cases treated without alkalis in Table II, and for those receiving adjuvant alkali therapy in Table III. In these tables are listed the organisms isolated before treatment, their sensitivity to streptomycin and also the relation of the streptomycin therapy to the appearance of resistant

TABLE II  
BACTERIOLOGY OF THE URINE IN CASES TREATED WITH STREPTOMYCIN WITHOUT ALKALIS

Case	Isolated Before Treatment		Result of Therapy	Isolated During Streptomycin Therapy			
	Organism	M.I.C.		Organism	M.I.C.	Previous Treatment	
						Gm.	Days
1	Paracolon bacillus	25	Failure	Paracolon bacillus	over 50,000	6	4
2	Friedländer's bacillus	12.5	Failure	Friedländer's bacillus	over 50,000	3.25	2
3	Aerobacter aerogenes	12.5	Failure	Aerobacter aerogenes	over 50,000	3	1
4	Escherichia coli	50	Failure	Escherichia coli	over 50,000	8	1
5	Friedländer's bacillus	6.3	Failure	Friedländer's bacillus	over 50,000	7	1
	Pseudomonas aeruginosa	12.5		Pseudomonas aeruginosa	over 50,000	19	3
6	Bacillus proteus	100	Failure	Escherichia coli	over 50,000	12.5	4
7	Escherichia coli	100	Cured				

M.I.C. = minimum inhibiting concentration in units (micrograms) of streptomycin per ml.

In the remaining six cases the bacilluria was essentially unaffected. Alkalis were not used in any of these cases and the urine remained acid throughout the streptomycin treatment. Resistant strains were isolated from all of these six patients during the streptomycin treatment. Resistant strains were also isolated from two of those who were treated with adjuvant alkalis. In one of the latter the resistant organism was isolated only once during the follow-up studies and this was not accompanied by other evidence of reinfection. In the other case the resistant strain first appeared two days after therapy ended and it is not certain whether the new strain was present but undetected before treatment or whether this was a reinfection with a new strain.

The bacteriological results in the indi-

strains corresponding to those present before treatment was started. The occurrence and streptomycin sensitivity of new strains during or after streptomycin treatment are also indicated.

*Sensitivity of Strains Before Treatment.* The Friedländer's bacilli and some of the strains of *Aerobacter aerogenes* were the most susceptible of the organisms isolated before treatment. They were inhibited by about 3-6 units per ml. The strains of *B. proteus* and two of the strains of *E. coli* were the most resistant of the gram-negative organisms and required 50-100 units. The remaining gram-negative bacilli including the two strains of *Pseudomonas aeruginosa* were intermediate in sensitivity and required 12.5-25 units per ml. for complete inhibition. Other and more extensive reports indicate that

TABLE III  
BACTERIOLOGY OF URINE IN CASES TREATED WITH STREPTOMYCIN AND ALKALIS

Case	Isolated Before Treatment		Streptomycin Therapy			First Negative Urine Culture (Hr. after First Dose)	Isolated after Streptomycin Treatment		
	Organism	M.I.C.†	Days	Gm.	Result		Organism	M.I.C.†	Days after Therapy Ended
8	<i>Aerobacter aerogenes</i>	12.5	7	28	Cured	18			
9	<i>Aerobacter aerogenes</i>	6.3	6	26	Cured	18			
10	<i>Aerobacter aerogenes</i>	3.1-6.3	5	20	Cured*	4	<i>Aerobacter aerogenes</i>	over 50,000	2
11	<i>Escherichia coli</i>	12.5	3	15.2	Cured	4	<i>Aerobacter aerogenes</i>	12.5	4*
12	<i>Escherichia coli</i>	12.5	5½	25.2	Cured	4			
13	<i>Bacillus acidilactici</i>	25	5½	32	Reinfection	4	<i>Escherichia coli communis</i>	12.5	38
14	<i>Escherichia coli</i>	12.5	2	12.6	Temporary improvement	12	<i>Aerobacter aerogenes</i>	over 50,000	2
15	<i>Friedländer's bacillus</i>	6.3-12.5	5	29.7	Temporary improvement	72	<i>Bacillus acidilactici</i>	12.5-25	12
16	<i>Friedländer's bacillus</i>	3.1	9	37	Cured	17	<i>Friedländer's bacillus</i>	12.5	34
17	<i>Bacillus proteus</i>	50							
17	<i>Friedländer's bacillus</i>	6.3	7	34.4	Cured	4			
18	<i>Bacillus fecalis alkaligenes</i>	12.5							
18	<i>Pseudomonas aeruginosa</i>	25	5	17	Cured	24			
19	<i>Staphylococcus albus</i>	50							
19	<i>Escherichia coli</i>	25	5	21	Temporary improvement	12	<i>Escherichia coli</i>	25	7
20	<i>Bacillus proteus</i>	100					<i>Bacillus proteus</i>	100	14
20	<i>Bacillus acidilactici</i>	25	6	26	Temporary improvement	24	<i>Escherichia coli</i> (intermediate)	100	5
21	<i>Streptococcus viridans</i>	100-500					<i>Streptococcus fecalis</i>	500-5000	3
21	<i>Bacillus proteus</i>	25-50	5	18.9	Temporary improvement	4	<i>Diphtheroids</i>	5000 or over	1
	<i>Bacillus acidilactici</i>	12.5					<i>Staphylococcus aureus</i>	12.5-50	8
	<i>Streptococcus fecalis</i>						<i>Streptococcus fecalis</i>	100-200	14
							<i>Staphylococcus albus</i>	25	14

\* Cultures were negative during further five and one half-month follow-up.

† Minimum inhibiting concentration in units (micrograms) of streptomycin per ml.

strains of the latter organism are often relatively resistant to streptomycin.<sup>12,13</sup>

*Occurrence of Resistant Strains.* Extreme resistance, that is, the ability to grow well in 50,000 units of streptomycin per ml., was demonstrated in nine strains isolated during or after the streptomycin treatment. Seven of these strains were identical in their morphological and cultural characteristics and in their biochemical reactions with the corresponding streptomycin-sensitive strains isolated before streptomycin treatment was started. Of the two other resistant organisms one was a strain of *A. aerogenes* obtained in Case 14 on the second day after treatment was stopped. The only organism identified in cultures of the urine of this case before the streptomycin treatment was a strain of *E. coli* that was inhibited by 12.5 units. In Case 6, a resistant strain of *E. coli* was found on and after the fifth day of streptomycin treatment. On several occasions prior to the

beginning of therapy in this case cultures were reported as yielding *B. proteus* and *E. coli*. The latter organism, however, was not found in the control cultures made during the three days preceding the streptomycin therapy and the earlier cultures were not available so that their sensitivity and cultural characteristics could not be compared with the post-treatment strains. In this small group of cases there seemed to be no correlation between the degree of sensitivity of the strains isolated before treatment and the development or appearance of resistant strains during or after streptomycin therapy.

*Mixed Infections.* A single organism was isolated and identified in fourteen cases and two distinct bacterial strains were recovered in seven cases before the streptomycin treatment was started. Alkalis were given to eight of the patients with a single strain and to six of those with mixed infections.

Among the eight with a single strain, essential cures of the infection were achieved in five cases, there was a reinfection in one and early relapse in the other two. Among the six patients who were treated with alkali and had mixed infections three were cured and the other three showed only temporary improvement followed by a relapse of infection with the same or with other organisms. This small number of cases tends to confirm the observation<sup>6</sup> that, in general, streptomycin treatment is less successful in patients with infections caused by a mixed flora than in those with a single susceptible organism.

*Appearance of New Strains.* New strains, distinct from those isolated from the urine before treatment, were identified in cultures obtained from five patients after the treatment with streptomycin and alkalis was ended. Some of the new strains were gram-positive bacteria having varying degrees of sensitivity to streptomycin. There were also four strains of gram-negative bacilli, one from each of four patients and only one of them (the *A. aerogenes* in Case 14) was totally resistant. The other new strains of gram-negative bacilli which appeared after the conclusion of treatment were similar in sensitivity to the pretreatment strains of similar organisms isolated from other patients.

*Streptomycin Levels.* Plasma and urine levels of streptomycin are given in the charts of the individual cases. They tended to vary in general with the dose of streptomycin and with the interval between injections. In most of the cases the plasma levels found throughout the treatment period and even on the first day of treatment were equal to or higher than the original *in vitro* sensitivity of the infecting organism. A progressive increase in the plasma level during the course of therapy was demonstrated in only three instances, in two patients who received one Gm. every four hours (Cases 4 and 5) and in one who was given 1 Gm.

every six hours. (Case 3.) The renal function was slightly reduced in Cases 4 and 5 but was normal in Case 3. In no instance, however, was the cumulative increase striking. Buggs and his co-workers<sup>14</sup> obtained a cumulative effect only in critically ill patients or in those with diminished renal function.

The levels of streptomycin found in individual specimens of urine collected daily showed marked variations ranging between 25 and 2,000 units per ml. No attempt was made to determine the total amount of streptomycin excreted or to follow the rate of excretion after single doses. Reports of such studies indicate that 50–70 per cent of the parenteral dose can be recovered from the urine.<sup>14–17</sup>

#### UNTOWARD REACTIONS

Four types of untoward reactions were encountered. The most frequent, although not the most serious, was pain and tenderness at the sites of injection. This was noted in almost every case, was usually mild, began during the latter part of the course of treatment and disappeared within one day after the injections were discontinued. Pain and tenderness severe enough to interfere with ambulation was experienced by seven patients. Three others developed severe pain, heat, redness and induration of the gluteal areas, which persisted for two to six days after the conclusion of therapy. This reaction prompted the premature interruption of therapy in two of them and necessitated a change to intravenous administration in the third.

Fever, probably attributable to the streptomycin developed in ten cases and occurred at various times after the beginning of treatment. It was first noted on the eighth day in one case but usually began during the second or third day. Four additional patients had fever during treatment which may have been caused by the infection.

Anorexia, malaise, headache, weakness, myalgia and arthralgia were among the symptoms experienced by five of those with fever. These symptoms usually disappeared within twelve hours after therapy was concluded.

A "histamine-like" reaction consisting of flushing and headache was experienced by three patients during intravenous injections that were probably given too rapidly. Transient syncope and clonic seizures accompanied this reaction in one patient. These were subsequently avoided by giving the intravenous streptomycin more slowly and in more dilute solution.

The most serious reaction was an acute labyrinthine disturbance which developed in one case after ten days of therapy. Nystagmus persisted for one week but vertigo on sudden motion of the head and unsteady gait have persisted with decreasing severity in this case for three months. Because of abnormal renal function and mild azotemia, this patient was given only sodium bicarbonate as an alkalinizing agent, potassium compounds being withheld because of the danger of retention and consequently disturbances of cardiac conduction. The possibility of a disturbed electrolytic balance inciting Ménière's disease must be entertained.

Two other patients developed mild vertigo which began forty-eight hours after the streptomycin was started and occurred only when they stood up. Therapy was immediately discontinued and the symptoms subsided within twelve hours. Three elderly patients who had hypertension and arteriosclerosis developed vertigo after the treatment was concluded, but the relation of the streptomycin therapy to their symptoms is dubious.

There were six patients who showed increases of the blood nonprotein nitrogen values during treatment. In only one patient who was quite dehydrated during the period

of treatment was this rise appreciable. The urine of four patients revealed a few granular casts during streptomycin administration, but this may have been due to concomitant fever and dehydration.

Untoward reactions similar to those observed in this series have been reported by others.<sup>8,16,18-20</sup> Brown<sup>20</sup> encountered twenty-three cases of labyrinthine disturbance among patients receiving prolonged treatment with streptomycin and Molitor observed similar disturbances of gait and posture in dogs.<sup>21</sup>

#### COMMENTS

Although streptomycin has a marked antibacterial effect *in vitro* on most of the gram-negative bacilli which are important in infections of the urinary tract,<sup>1,12,13,22</sup> the results of therapy of such infections have not been uniformly favorable.<sup>1,5-9</sup> In the 409 cases collected by the Committee on Chemotherapeutics and Other Agents of the National Research Council<sup>6</sup> the over-all recovery rate was only 42 per cent. A similar recovery rate was obtained in the present small series.

Most of the possible causes for the failures have been outlined by Reimann, Price and Elias.<sup>1</sup> Among them the rapid development of streptomycin-fastness by the infecting organism is one of the most important.<sup>7-10,14</sup> There are numerous reports which demonstrate the relative ease with which various organisms can be made to acquire streptomycin resistance *in vitro*<sup>23-31</sup> and Knop<sup>11</sup> has produced fastness rapidly in thirteen strains from urinary tract infections by using urine containing various concentrations of streptomycin as the culture medium.

The findings in the first six cases illustrate very strikingly the significance of this factor in the treatment of urinary tract infections with streptomycin. In these cases resistant strains, indistinguishable culturally and biochemically from the pretreatment sensitive

strains, were obtained after from one to four days of treatment.

That dosage alone was not the primary factor in these cases is indicated by the fact that increases in dosage to almost the maximum tolerated amounts did not prevent the appearance of resistant strains.<sup>7</sup> Attempts were made to produce similar degrees of resistance in some of the pretreatment strains from these cases by cultivation in streptomycin containing media. From thirteen to forty-nine daily transfers on solid media were required. During these studies, isolated colonies were occasionally observed to grow well in the early transfers in concentrations of streptomycin which, though low, were adequate to inhibit the remainder of the inoculum and no growth was observed on the plates containing some lower concentrations of the antibiotic. Such colonies, after preliminary subculture in streptomycin-free media, were found to be totally resistant. These *in vitro* studies, which are reported in detail elsewhere,<sup>31</sup> suggest that resistance may be acquired by the same strain either by gradual adaptation or by sudden appearance of resistant forms. The *in vitro* studies suggest that the latter ones are mutants having the new characteristics. In the patient, however, it is not possible to say whether the same is true or whether the resistant form was originally present and was merely selected after elimination of the sensitive cells through exposure to streptomycin.

Streptomycin activity is much greater *in vitro* in an alkaline than in an acid medium.<sup>32-34</sup> Abraham and Duthie,<sup>34</sup> tested the activity of streptomycin against *Strep. pyogenes*, *Strep. fecalis*, *Staph. aureus*, *B. proteus*, *Bact. coli*, *Bact. typhosum* and *Ps. pyocyanea* using both large and small inocula. They found that an increase in the pH of the media from 6 to 8 increased the activity of streptomycin by 2 to 67-fold. A suggestion of the possible influence of this factor *in vivo*

was obtained in Case 6. The urine was alkaline before treatment in this case owing to a *B. proteus* infection. When streptomycin was started, that organism was rapidly suppressed and then completely eliminated although it was not highly sensitive. The urine then became acid and a resistant *E. coli* appeared. In view of this observation and the more convincing *in vitro* evidence, an attempt was made to determine whether alkalization of the urine during streptomycin therapy would increase the efficiency of treatment and reduce or prevent the development of resistance.

The results, as summarized in Table 1, suggest that alkalization did, indeed, have a very favorable influence. Of fourteen patients in whom the urine was kept alkaline throughout the period of streptomycin therapy, eight were apparently cured of their infection. Cultures of urine obtained a few hours after the first dose of streptomycin were sterile and the urine has remained bacteria-free during the follow-up period. In the remaining six cases, the infection of the urine cleared during the treatment and for varying periods thereafter. The organisms that were found after the treatment in most of these cases were different from the pretreatment strains and, for the most part, were as sensitive to streptomycin as similar strains that have not been exposed to the antibiotic.

The source of the new strains which appeared after the course of alkalis and streptomycin is not clear. They may have been present and could not be isolated from pretreatment urine specimens by the methods used. If this were true, the findings would suggest that alkalization not only enhanced the action of the streptomycin but also prevented the development of resistant strains in most cases. This possibility cannot be dismissed since some of the strains isolated after treatment with alkalis and streptomycin were similar, both culturally

and in their sensitivity, to the corresponding pretreatment strains.

It is to be borne in mind that the present treatment was directed against the infections and not against the underlying defects which made these infections possible or which contributed to their persistence. The organisms concerned are similar to those normally found in the bowel and sources of reinfection with such organisms are always present, provided that the tissues remain susceptible, the pathways of infection remain open or the possibility of stasis persists. In some of the present cases; remediable defects could not be found. Elimination of infection as early as possible in such cases is of paramount importance in order to limit the damage to the tissues and maintain renal function. Any possible means to accomplish this end is worth while. When mechanical defects are found and can be corrected, that obviously should be done. Antibacterial therapy may still have an important place before, during and after such procedures.

In the treatment of urinary tract infections the question arises whether it is the concentration of the active agent in the urine or in the tissues that is more important. The present data offer no clear answer. It would seem, however, that the concentration and other properties of the agent in the urine are of considerable significance because the greatest effect of the alkalization must have been in the urine. It seems unlikely that the pH of the blood or of the infected tissues was altered enough to influence streptomycin activity significantly.

#### CONCLUSIONS

The results in the present series of cases of urinary tract infections suggest that the maintenance of an alkaline reaction in the urine throughout the period of streptomycin therapy increases the efficacy of the streptomycin and reduces the likelihood of the de-

velopment of streptomycin-fastness in the infecting organisms.

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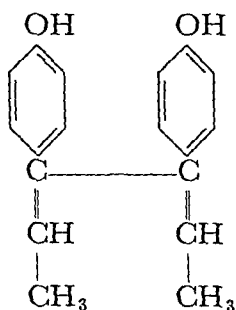
# Dienestrol\*

## *Another Synthetic Estrogen of Clinical Value*

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AN opportunity to study the clinical usefulness of dienestrol was afforded us\* in November, 1944, following brief reports of favorable results in British journals.<sup>1,2</sup> This synthetic estrogen is a hexadiene and it differs from the stilbestrol derivatives and from the other synthetic estrogenic materials on the American market at present. Its chemical and physical properties were recorded in 1938 and 1939 by Dodds et al.<sup>3,4</sup> Emmens<sup>5</sup> found in 1938 that its oral activity in mice was higher in relation to its subcutaneous dose than in any other estrogen yet tested. Barnes,<sup>1</sup> using it to inhibit lactation in women, considered that dienestrol was effective in dosage about one-tenth that of stilbestrol. Because of this known high potency per mg. the original supplies were in tablets of 0.1 mg.

The formula of dienestrol:



Our observations were made on a group of twenty-one women out-patients suffering

\* We are glad to express our gratitude to Dr. C. W. Sondern, of the White Laboratories, Inc., Newark, N. J., for generous supplies of dienestrol.

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from the complaints well known as characteristic of the climacteric syndrome. Only two had had no prior experience with estrogenic therapy. Most of them had been under observation for variable periods of time and had used one or more estrogens, natural or synthetic. Their success with other estrogens had been variable, usually satisfactory when the dose had been maintained at an adequate level. Three had had definite nausea and emesis when using barely adequate doses of diethylstilbestrol. Consequently, both clinician and patient had a basis for comparing the results following dienestrol and other estrogens. Exact dose comparisons were not made because this would have required prolonged periods of use of each substance at the minimum effective level if fair relative statements were to be made. Microscopic study of stained vaginal smears was made throughout, and the usual changes toward cornification of shed epithelial cells indicated estrogenic activity as compared with pre-treatment conditions.

The important data are presented in tabular form relating, however, to only thirteen women since eight were unable to report to the clinic regularly enough to justify conclusions about the effectiveness of the therapy. Excellent or completely satisfying results were reported by five women with doses ranging from 0.1 to 0.6 mg. daily. Seven patients secured good results but relief of



symptoms was not complete; doses varied from 0.1 to 0.5 mg. daily in this group. It is likely that some of this latter group would have had excellent results if circumstances had allowed us to follow them after slightly higher doses, as we did in some of the first five mentioned. An unsatisfactory result occurred in only one case and this woman preferred to discontinue trial of dienestrol at only 0.3 mg. daily.

It will be noted that in most of these women the menopause began spontaneously. The only apparent difference in results in this connection was seen in the two women whose climacteric syndromes followed irradiation and who had adequate trial of dienestrol. They secured less complete relief from the treatment than did most of our patients. In both cases there is reason to believe that the irradiation was not thorough enough to cause complete inactivation of the ovaries, a circumstance which has repeatedly seemed to cause a syndrome difficult to relieve.

Our twenty-one patients reported no nausea, emesis, nor other unpleasant side reactions from dienestrol in dosage up to 0.5 mg. twice daily, but usually not over 0.5 mg. daily. As mentioned, three patients had had nausea and emesis following diethylstilbestrol in minimum effective dosage. On the other hand, the use of dienestrol has not been followed by the spontaneous reports of well-being which were made following use of some of the natural estrogens.<sup>6</sup> Based on an admittedly small series, we think dienestrol is the most satisfactory synthetic estrogen with which we have had experience.

Since 0.1 mg. dienestrol secured acceptable results in only three cases and 0.2 mg. would have secured such results in six of the twelve favorable results, we suggest that the initial trial dose be 0.2 mg. and that the minimum tablet might well be this

size. Similarly, since three of the twelve required 0.5 or 0.6 mg. per day, a 0.5 mg. tablet would be a convenient and probably economical size.

SUMMARY

Clinical trials of dienestrol for relief of climacteric symptoms in thirteen women indicate that doses of 0.2 to 0.5 mg. daily are adequate, dependable and tolerated without unpleasant side effects.

MENOPAUSE

Patient	Age	Spontaneous	Surgical	Radiation	Dienestrol mg./day	Results	
						Excellent	Good
Ac....	55	#			0.2		#
An....	49		#	#	0.6	#	
Er....	29			#	0.3		#
Ha....	47	#			0.3	#	
Ke....	36	#			0.5		#
Ko....	54		#		0.3		#
Na....	53		#		0.2	#	
Re....	50	#			0.5		#
Sc....	56	#			0.1		#
Sm....	38	#			0.2	#	
Sw....	49	#			0.1		#
Va....	31	# <sup>a</sup>			0.1	#	
We....	39			#	0.3		

<sup>a</sup> Irregular menses, climacteric symptoms.

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## Bacillus Pyocyaneus Infections<sup>\*</sup>

### *A Review, Report of Cases and Discussion of Newer Therapy Including Streptomycin<sup>†</sup>*

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**D**URING the last four years penicillin has been used in clinical medicine and surgery in increasing amounts, not only for the treatment of infections due to gram-positive organisms but also as "prophylactic" therapy in an attempt to prevent infection. This period has been marked by a growing number of cases of secondary infections due to such gram-negative organisms as the *B. pyocyaneus*. This did not occur during the sulfonamide era because these latter drugs are much less specific in their bacteriostatic properties and tend to prevent the growth of gram-negative bacilli. On the other hand, a relatively minor contamination with gram-negative organisms in a patient treated only with penicillin will often be followed by a flourishing infection; as one of an apparently mutually antagonistic pair is efficiently removed, the other thrives. We are now beginning to see the converse of the same situation; as the equally specific antibiotic streptomycin is being widely used more and more unexpected infections with gram-positive organisms are discovered.<sup>149</sup>

It is the purpose of this paper to review the subject of infection with the *B. pyocyaneus*. This seems to be a particularly

appropriate time for such a summary, not only because it is a short while after the introduction of streptomycin, another agent effective in treatment, but also because the results of approximately ten years' experience in the use of the sulfonamides are now available. We are reporting several cases in which we have treated the patients with each of these agents.

#### LITERATURE

Since the isolation of the *B. pyocyaneus* in 1882 by Gessard<sup>1</sup> the literature has not been extensive and in general has been commensurate with the frequency with which the organism is found as a human pathogen. Most of the articles consisted of case reports of various types of infections. In Fraenkel's classic paper<sup>2</sup> the general pathological picture was graphically portrayed. General reviews of the subject were written by Waite<sup>3</sup> (older literature to 1908) and more recently by Lode<sup>4</sup> (1929) and Epstein and Grossman<sup>5</sup> (1933). Other reviews of localized infections, endocarditis (Fish, Hand and Keim,<sup>48</sup> Moragues and Anderson<sup>50</sup>), meningitis (Evans,<sup>58</sup> 1936), gastrointestinal infections (Bezi,<sup>37</sup> 1933), corneal ulcer (Joy,<sup>115</sup> 1942), etc., are available.

<sup>\*</sup> From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

<sup>†</sup> Examinations of the pathological material were carried out by Dr. Rudolph Osgood (Cases II, III, IV and X) and Dr. Charles Branch (Case I).

BACTERIOLOGY<sup>4,6,7</sup>

The *B. pyocyaneus* (*Ps. aeruginosa*, *Ps. pyocyanea*, *Bacterium aeruginosum*) is a slender gram-negative rod 1.5–3.0 by 0.5 micra which exhibits considerable variation in morphology and cultural characteristics. It is motile, non-sporing and non-acid-fast. It grows readily on the usual media at optimum temperatures of from 30–37°C. and pH from 6.6 to 7.0. It is aerobic and forms acid from glucose but from no other sugar; no gas is produced from carbohydrate fermentation. Some strains produce two pigments,<sup>8,9,10</sup> pyocyanin (blue, soluble in water and chloroform) and fluorescein (yellow or green, fluorescent, soluble in water, insoluble in chloroform). Other strains produce only one of these pigments and a few are entirely colorless. Old cultures may change from bluish-green to reddish-brown, black or yellowish-brown as oxidation alters the chemical structures of the pigments. The organism has been called “the bacillus of blue-green pus”<sup>1</sup> because of this characteristic discoloration which is imparted to exudates by its pigments.

The organism produces a proteolytic enzyme which enables it to hydrolyze gelatin, fibrin, casein and albumen. This, together with the characteristic site of localization of the organisms in the smaller blood vessels with consequent thrombosis and occlusion, partly explains the tendency to production of infarct-like areas of necrosis with a minimum of inflammatory reaction which has been so frequently noted.<sup>2</sup>

*B. pyocyaneus* is capable of exciting production of various antibodies in infected animals and man. Of these the agglutinins are the best studied. They appear early, are easily identified and hence are of definite diagnostic value. A titer higher than 1:30 is rarely encountered in normal subjects,<sup>11</sup> while titers as high as 1:500–1000 are common in the presence of infection. Owing to the great variation in antigenicity the pa-

tient's own strain of organisms should be used as the agglutininogen.

*B. pyocyaneus* is found on the normal human skin, particularly in the axillary and anogenital regions,<sup>4</sup> and is uncommonly cultured from the stool.<sup>11,12</sup> It may be grown from the air, especially in surgery wards containing patients with infected wounds.<sup>101</sup> In some sections of the world it is easily discovered in the drinking water which thus provides it an easy access to the gastrointestinal tract.<sup>11</sup> It may contaminate solutions of penicillin,<sup>101</sup> boric acid,<sup>132</sup> fluorescein,<sup>120</sup> procain<sup>28</sup> and other anesthetic agents (see section on meningitis) and “sterile” distilled water and thus be carried to a favorable location for initiation of infection.

The problem of contamination of penicillin solutions by resistant organisms is a real one;<sup>101</sup> there is always danger of secondary infections, as when the agent is used for intrathecal injection in the treatment of meningitis or for instillation into the various serous cavities. One occasionally encounters an instance of abscess formation at the site of injection in the muscle which has a similar pathogenesis. Strict asepsis must be maintained in the preparation and injection of penicillin solutions.

## PYOCYANEUS SEPSIS

It is now firmly established that the *B. pyocyaneus* may invade the blood stream and produce sepsis although it should be emphasized that its usual rôle is that of a relatively avirulent secondary contaminant in superficial wounds. The first reports of cases in which positive blood cultures were found during life were those of Finkelstein<sup>13</sup> (1896) and of Brill and Libman<sup>14</sup> (1899). Bacteremia most frequently occurs in infants and children and in adults afflicted with chronic debilitating diseases. Cases (I, II, III, IV and IX) described in this paper are excellent examples of adult infections in which the *B. pyocyaneus* sepsis occurred as a termi-

nal complication in patients already ill with fatal diseases. In infants and children,<sup>2,39</sup> the skin is most commonly the portal of entry for the organism; in adults invasion is also frequently through the genitourinary tract.<sup>42-45</sup> The gastrointestinal tract is the site of entry in a considerable number of patients, both infants and adults. Enteric infection which, contrary to the usual predilection, may be present in otherwise healthy adults, may produce a clinical picture which is indistinguishable from that of typhoid fever except for its short duration and almost invariably benign course.<sup>15,16</sup>

There are interesting reports of sepsis arising in unusual locations. Wassermann<sup>17</sup> described an epidemic of eleven cases of umbilical infection of the newborn all of which resulted in death. Several cases of postpartum infection with bacteremia<sup>18,19,55</sup> have been reported. Kraus and Hunter<sup>97</sup> reported a case apparently of infection of the fetus through the placenta. The mother had chills and fever during labor; the baby was born with a rash and died twenty hours after birth with sepsis. The mother had *B. pyocyaneus* in her stools, but not in the lochia; no blood cultures were taken during the chills.

The clinical picture in sepsis due to the *B. pyocyaneus* is usually not different from that produced by many other types of organisms, and the diagnosis is of necessity based on culturing the bacillus from the blood. There are chills, high fever, prostration, petechial skin lesions, jaundice and embolic manifestations in various organs including splenomegaly, just as in any septic infection. Agranulocytosis, with or without angina,<sup>20-24</sup> has been observed occasionally and has been the subject of several special reports. Secondary thrombocytopenic purpura with resulting hemorrhages<sup>26</sup> may complicate the picture, as in our Case II (H. B.). There is one phenomenon, however, which when it occurs during the course of

an apparent sepsis should lead one to suspect strongly the causative rôle of the *B. pyocyaneus* on clinical grounds. This is the finding of gangrenous skin lesions ("ecthyma gangrenosum"),<sup>22,25,137</sup> particularly in the anogenital region and the axillae. Fraenkel<sup>2</sup> was able to make the diagnosis clinically from the presence of these lesions with a high degree of accuracy.

The course is generally rapidly downhill, with the exception cited,<sup>15,16</sup> and usually terminates fatally<sup>2</sup> despite treatment. In all likelihood this is as much an indication of the general debility of the usual patient as it is of the virulence of the organism. Secondary localization of infection, particularly in the meninges and on the heart valves, may add other symptoms which complicate the clinical picture.

CASE I. Pneumococcic pneumonia and empyema were present in a woman with paraplegia who was debilitated, bedridden and incontinent. (Fig. 1.) *B. pyocyaneus* infection in large decubitus ulcers and later development of gangrenous cystopyelonephritis and sepsis due to *B. pyocyaneus* were followed by death.

R. K., a fifty-two-year-old female, entered on December 26, 1944, complaining of a cough productive of yellow, thick sputum of six weeks' duration, and bilateral decubitus ulcers of more than two months' duration.

Four years prior to admission she entered the hospital with ataxia, paresis of the lower extremities and incontinence of urine and feces of one year's duration. There were vague sensory disturbances and nystagmus. She signed herself out before a definite diagnosis was made, although multiple sclerosis was considered the best possibility. She remained at home, bedridden and incontinent, until the present admission.

Six months prior to admission, following a head cold, she developed a cough which soon became productive of thick, yellow sputum, occasionally blood-flecked. There were no chills, sweats or pleuritic pains. No specific treatment was given. During the month prior to admission the cough became worse and progressive or-

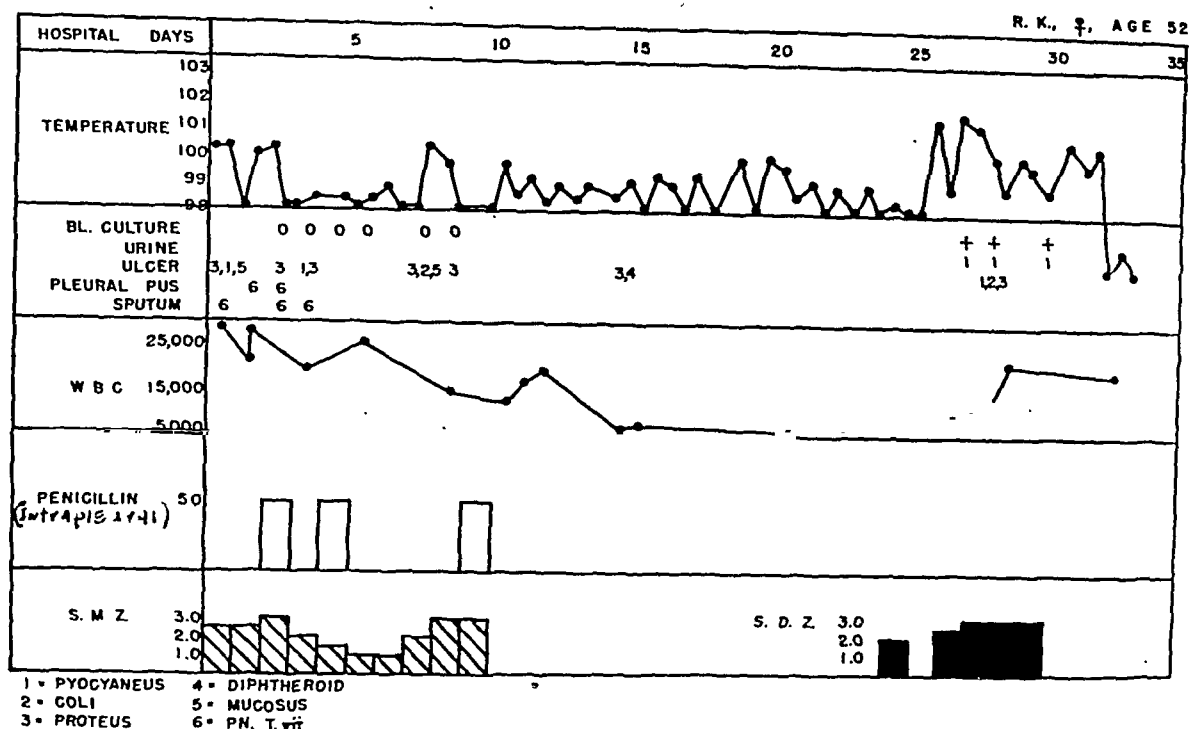


FIG. 1. Case 1. Infection with *B. pyocyaneus* in large decubitus ulcers followed by gangrenous cystopyelonephritis and fatal sepsis.

thopnea developed. Because of the orthopnea and incontinence, she spent the two weeks before coming to the hospital sitting on a special rocking chair with a built-in toilet seat. During this period, two previously small bed sores on her buttocks became much larger and more painful. She developed marked stubbornness, occasional delirium and frequent crying spells. One week before admission, she began to have marked edema of the lower extremities.

Physical examination revealed the patient to be well developed but emaciated and she appeared chronically ill. She preferred to lie on her side with her lower extremities flexed on her abdomen. On each buttock was a large ulcer, 7 to 8 cm. in diameter, with a purplish-black, necrotic, sloughing center and red, swollen, tender periphery. There was flatness to percussion and distant bronchial breath sounds at the left base, posteriorly, with shift of the mediastinum to the right. The heart was otherwise normal. The abdomen was normal. There was marked soft pitting edema of the lower extremities. There was a right horizontal nystagmus. Paralysis of the lower extremities with flexion contracture was present. Deep tendon reflexes were absent in the lower extremities but normal

in the upper extremities. Abdominal reflexes were absent. There was no Babinski. There was marked emotional lability but the sensorium was clear.

Pneumococcus type vii was cultured from the sputum and the thick, green pus aspirated from the left pleural cavity. There was a slight albuminuria, with marked pyuria, and slight microscopic hematuria throughout. *B. pyocyaneus*, *B. coli* and *B. proteus* were cultured from the urine during the latter part of the course. The white blood count on admission was 29,400 per c. mm., with 72 per cent polymorphonuclear leukocytes. There usually was a well marked leukocytosis, ranging from 13,000 to 26,000 white blood cells per c. mm. of blood, although during the eleven days prior to the development of the pyocyanus bacteremia, which preceded death, the white blood count was essentially normal. A moderate anemia persisted, with hemoglobin ranging from 11.5 to 8.5 Gm. per cent, and hematocrit from 32 to 25 per cent. There was a mixed flora in the decubitus ulcers; *B. pyocyaneus*, *B. coli* and *B. proteus* were the principal organisms. During the latter part of the course, *B. pyocyaneus* predominated in the cultures.

Treatment of the pneumococcus pneumonia in the hospital was begun with sulfamerazine by mouth and was continued for nine days. Great difficulty was experienced in obtaining an adequate fluid intake. The empyema was treated by repeated aspirations of the pus and instillation of penicillin into the pleural cavity. Gradual débridement of the decubitus ulcers was carried out with repeated irrigation of the craters with a solution containing a mixture of 10 per cent urethane and 1 per cent sulfanilamide. With this therapy she seemed to improve somewhat, although she was drowsy usually and required tube feeding. The ulcers cleared considerably, the necrotic tissue being eliminated, and presented moderately clean contracting granular bases. A Foley catheter was inserted into the bladder soon after admission. Because of a dilated urethra, there was some difficulty in preventing spontaneous extrusion of the inlying catheter from the bladder. On the twenty-third hospital day, she complained of severe, lower abdominal, steady pain. Two days later, a small amount of gross blood and pus was noted draining from the bladder. The following day she began to run a rapidly downhill course, characterized by spiking fever, jaundice, increasing stupor and repeated vomiting of coffee-ground material. *B. pyocyaneus* was cultured from the blood on three different days. Nitrogen retention developed. On the thirty-second hospital day, a right anterior pleural friction rub was noted. She died on the thirty-fourth hospital day after a terminal fall in body temperature to 95 and 96°F.

*Gross Pathology. Kidneys:* The right kidney weighed 260 Gm. and was distinctly enlarged. The capsule was slightly thickened, stripped with ease, revealed a grossly irregular, finely granular, reddish-brown surface, marked by several varying-sized, elevated areas containing numerous minute, white, elevated foci, which, on section, were found to extend down through the cortex to involve the pyramids in radial streaks. Section revealed an edematous, bulging surface everywhere marked by the white radial streaks. From the pyramids a small amount of purulent material was expressed. The mucosa of the pelvis was roughened and necrotic. The pelvis contained a small amount of sanguineous

pus. The ureter was dilated and measured 6 mm. in diameter. No ureteral obstruction was found.

The left kidney weighed 300 Gm. Externally it closely resembled its fellow on the right. On section, two entirely separate pelves and ureters were found. The upper pelvis and its ureter were normal. The mucosa of the lower pelvis was gangrenous with a large amount of hemorrhage in the tissues. The renal substance on the left resembled that on the right. The two ureters entered the bladder through separate orifices.

*Urinary Bladder:* The mucosa was markedly hemorrhagic and necrotic. There was approximately 20 cc. of bloody pus in the bladder.

*Pleural Cavities:* The right was completely obliterated by fibrinous adhesions which were easily separated. The left was completely obliterated by very dense adhesions which were separated only by sharp dissection. At the posterior base there was a cavity 10 cm. in diameter from which air under pressure escaped when opened. The lining of the cavity was fibrinous. No bronchial communication was found.

*Gastrointestinal Tract:* On the greater curvature of the stomach there was a shallow superficial ulceration of the mucosa, 8 mm. in diameter. The base was clean and there was no necrotic membrane. No other lesions were seen in the gastrointestinal tract.

The lungs, heart, and other organs were not remarkable grossly.

The predominating organism cultured from the urinary tract and empyema cavity was *B. pyocyaneus*.

**MICROSCOPIC PATHOLOGY.** *Urinary Bladder:* The mucosa was almost completely replaced by a heavy infiltration with polymorphonuclear leucocytes and fibrin. There were many large colonies of organisms in this membrane. There was extensive thrombosis of the capillaries overlying the muscularis. The muscularis was edematous and the muscle fibers fragmented in several places; slight infiltration with neutrophils extended into the superficial layers of the muscularis.

*Kidneys:* The pelves resembled the urinary bladder. Approximately four-fifths of the kidneys themselves were completely destroyed, riddled with extensive discrete and confluent abscesses, which extended in a radial fashion

from the pelvis, and which obliterated the normal architecture. Much of the remaining tissue was edematous and in a state of semi-liquefaction necrosis, with slight neutrophilic infiltration from adjacent areas of suppuration. Numerous vessels contained bacteria-laden thrombi, especially near the pelvis.

*Stomach:* Section through the ulcer showed that the normal mucosa abruptly gave way to the shallow crater which extended only to the muscularis. The base of the ulcer was covered with a thin network of fibrin, in which there were many neutrophils and colonies of bacteria. There were no thrombi or emboli in the vessels immediately underlying this area, although the general histological appearance strongly suggested an embolic origin. The muscularis was edematous and the overlying serosa was normal.

*Lungs:* In general, the alveoli contained only a small amount of coagulated albuminous precipitate in which were very few inflammatory cells. Occasional small vessels were completely occluded with masses of disintegrating fibrin, neutrophils and large colonies of bacteria. In such areas the vessel walls were partially or completely destroyed by an acute inflammatory and necrotic process, and the surrounding alveoli were distended with large numbers of neutrophils and erythrocytes, fibrin and colonies of organisms. There was a small amount of neutrophile-laden mucus in the bronchi and slight edema and infiltration of the walls.

*Spleen:* Very little of the normal structure remained. There were extensive capillary thromboses, surrounded by zones of coagulation and liquefaction necrosis, heavily infiltrated with polymorphonuclear leukocytes, macrophages and some lymphocytes. There were scattered hemorrhages and much fibrin present. Many small colonies of organisms were seen in the thrombosed vessels and areas of necrosis.

*Liver:* The liver cells were swollen, stained faintly and acidophilically with poorly defined nuclei. This property was more marked about the central veins; about these vessels there was early necrosis, with only occasional patches of beginning neutrophilic infiltration.

Other changes included slight hypertrophy of the myocardium with moderate coronary atherosclerosis and myocardial fibrosis, and in

the adrenals, small areas of focal necrosis and multiple small infected emboli.

*Final Pathological Diagnoses:* Acute ulcerative cystitis; acute bilateral pyelonephritis; *B. pyocyaneus* septicemia, with embolic lesions in the lungs, spleen, stomach and adrenals; encapsulated thoracic empyema, left; early central necrosis of the liver and bilateral advanced decubitus ulcers. (Sections of the brain and spinal cord were not available at this time so that the primary central nervous system lesion is unknown.)

CASE II. This is a case of *B. pyocyaneus* septicemia occurring during treatment with penicillin for secondary infection of the skin in a boy with an acute exacerbation of chronic disseminated lupus erythematosus. (Fig. 2.) Sterilization of the blood stream was carried out with streptomycin. Congestive heart failure, thrombocytopenic purpura and meningitis were followed by death.

H. B. was a seventeen-year-old schoolboy who was transferred from a neighboring hospital with a progressive generalized weeping, crusted rash and high fever. The family history and past history were irrelevant.

Two years prior to admission he developed an area of erythema of "butterfly" distribution over both cheeks and bridge of the nose, which persisted for several months despite various local applications and injections of bismuth subsalicylate intramuscularly. Nineteen months prior to admission, while the lupus erythematosus was still active, he was given sulfathiazole and later sulfamerazine for a dental abscess. He reacted to these drugs with fever, nausea and vomiting. After extraction of the offending teeth, there was oozing of blood from the gums for two weeks. Following this, however, he improved and the rash virtually disappeared in a short time. Sixteen months prior to admission, a tonsillectomy was also followed by a small amount of bleeding from the fossae for several weeks. There were no other manifestations of a hemorrhagic tendency.

Five months prior to admission, he incurred a severe generalized sunburn. A recrudescence of the lupus erythematosus quickly developed, and the rash spread to the forehead, ears, scalp, neck and back. During the next three months, the process persisted despite treatment and the hands

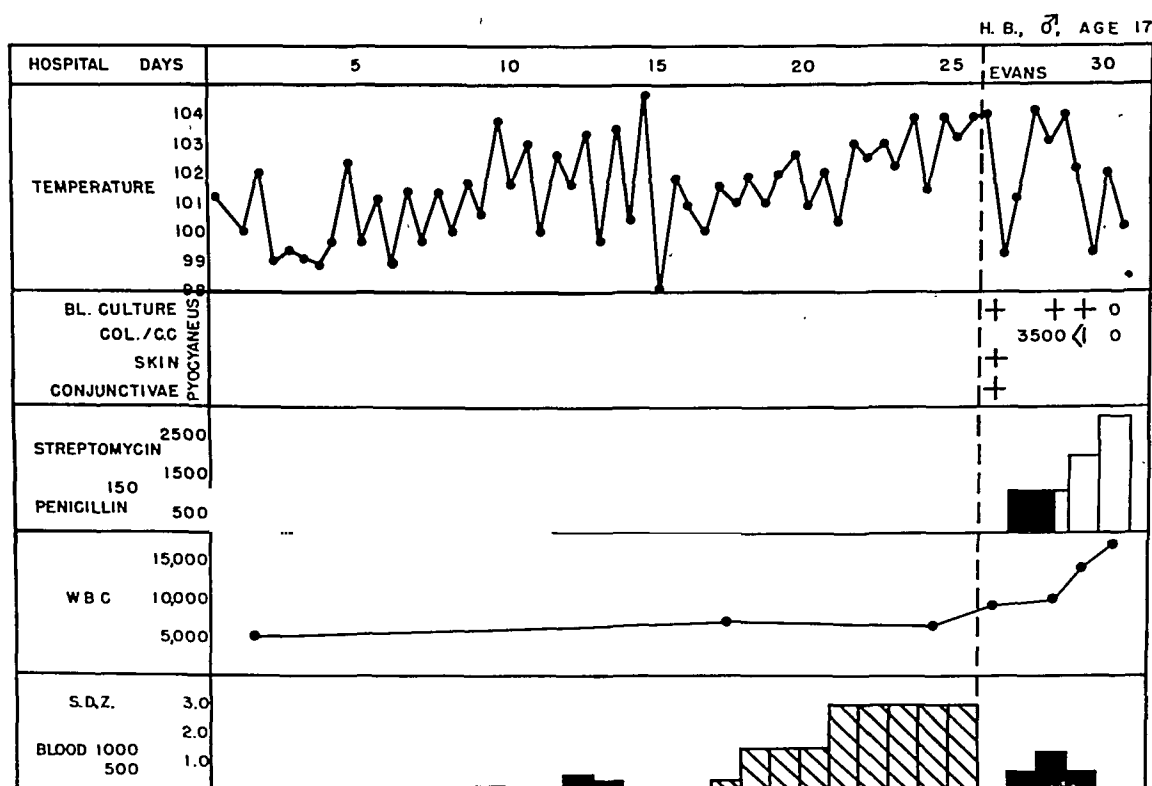


FIG. 2. Case II. Fatal septicemia with onset during penicillin treatment for secondary skin infection in chronic disseminated lupus erythematosus.

and fingers became involved. Seven weeks prior to admission, after considerable scratching because of pain, burning and itching, the rash became weeping and crusted. Irregular fever as high as 102°F. persisted.

Twenty-six days prior to admission he entered the referring hospital. He was febrile but only "moderately" ill. There were crusted, weeping papular lesions, 2 to 10 mm. in diameter, scattered over the anterior surface of the chest, neck and hands. A similar, but more pronounced and confluent rash covered the face, ears and scalp. The mucous membrane of the nose was edematous, red and bleeding. The soft palate was covered with discrete, oozing, red papules resembling the skin lesions. There was a moderate anemia and normal white blood cell count.

Penicillin, 160,000 units daily, was administered for eleven days, with only temporary benefit in the beginning. During the last week in this hospital, sulfadiazine in small doses was given. He received three small transfusions, totaling 650 cc. of whole blood. He continued to run a septic temperature, his skin lesions were progressive and his general condition grew worse.

On admission to the Evans Memorial he appeared emaciated, debilitated and severely ill. The lesions on the face, scalp and ears were covered with sanguino-purulent exudate, much of which was dried and crusted. There was marked edema of the face, especially of the periorbital regions. There was a purulent conjunctivitis; the eyes were swollen shut. There were numerous 4 to 5 mm. vesicles filled with serous or serosanguineous fluid on an erythematous base scattered over the chest, abdomen, upper extremities, thighs and flanks. The palmar surfaces of the hands and fingers and the V-area of the neck were covered with painful erythematous papules, often confluent. The nails were broken. There was subungual infection. The mucous membranes of the nose and mouth were crusted and bleeding so that examination was inadequate. The lungs were normal. There was a marked sinus tachycardia (rate 150) with a pronounced diastolic gallop. The heart was of normal size and there were no murmurs present. Blood pressure was 104/54 (left arm). The abdomen was normal. There was moderate bilateral



costovertebral tenderness. There were no neuromuscular abnormalities; the neck was supple.

Urine averaged 6 Gm. per liter of protein (4+), contained no sugar, ketones or bile. There were 5 to 30 leukocytes and 5 to 30 erythrocytes per "high-dry" microscopic field (uncentrifuged specimens). Granular, erythrocytic and leukocytic casts were present in large numbers. Hematocrit was 19.5 per cent and hemoglobin 5 Gm. per cent. Four days later, as a result of transfusions, these had risen to 42 and 13.2 Gm. per cent, respectively. Total leukocytes in the blood were 9,800 per c. mm. with 75 per cent polymorphonuclears, 17 per cent lymphocytes and 8 per cent monocytes on admission, and steadily rose to 17,300 four days later. Blood platelet counts varied from 41,000 to 67,000 per c. mm. Blood clotting time (3-tube method) was twelve minutes, forty-five seconds (normal six to twelve minutes). Bleeding time (Duke method) was two minutes, forty seconds. (This procedure was probably inaccurate because of inability to find a skin area completely free of lesions.) Clot retraction was 47 per cent of plasmatocrit (normal 80 per cent or more). Blood non-protein nitrogen was 47 on admission, and steadily rose to 108 on the fourth day. Blood total proteins were 6.2 Gm. per cent, with 1.25 Gm. albumin and 4.96 Gm. globulin on admission. Carbon dioxide combining power varied from 29 to 39 volumes per 100 cc.

Three blood cultures were positive for *B. pyocyaneus*. On the second day, when treatment with streptomycin was begun, there were 3,500 colonies per cc.; one day later there was less than one colony per cc. On the third day of treatment, the blood culture was sterile (day of death). *B. pyocyaneus* was cultured from the pus in the conjunctival sacs and from several of the skin lesions.

Bedside chest x-ray on the second day revealed suggestive evidence of cardiac enlargement and patches of hazy density radiating from the hilar regions to both mid-lung fields.

Electrocardiogram on the second day showed a sinoauricular tachycardia of 150 beats per minute, low voltage and slurring of the Q-R-S complexes, inversion of the T waves in leads 1 and 2, and a normal axis. Two days later there was moderate right axis deviation, the T waves

in lead 1 were upright with slightly high origin, and there was a Q wave in lead 1.

Streptomycin, 250,000 units every three hours subcutaneously, was started approximately forty hours after entry, after the nature of the bacteremia became known. The dosage was increased to 500,000 units every three hours ten hours before death. A total of 5,810,000 units was given. Ten doses of penicillin, 20,000 units every three hours intramuscularly, were given early in the course, before the blood culture report had been received, but this was discontinued when streptomycin was started.

Supportive treatment consisted of 2,000 cc. of whole blood, in four transfusions of 500 cc. each, intravenous and subcutaneous fluids in the form of physiological saline and 5 per cent glucose solutions, and oxygen by means of a tent and nasal catheter. Warm saline compresses were followed by the application of aquaphor to the skin lesions several times daily. The conjunctivae were irrigated with a streptomycin solution, 5,000 units per cc., in physiological saline. Cedilanid (lanatoside C) was given in five doses of 0.4 mg. each intravenously on the second day, when it appeared that congestive heart failure was present, and was continued in maintenance doses until death.

During the period at the hospital before the exact diagnosis was known, he steadily grew worse and became irrational and semi-stuporous. Temperature, which was 99°F. rectally on admission had risen to 104.2°F. twenty-four hours later. The skin lesions tended to spread and he became cyanotic and dyspneic. On the second day, when a large subcutaneous ecchymosis appeared on the abdominal wall within a very short time, and later that day the skin lesions began to assume a hemorrhagic appearance, it became evident that thrombocytopenic purpura was present. Within twenty-four hours after streptomycin was begun on the second day his temperature returned to normal, the skin lesions improved dramatically, with much decrease of exudation and inflammatory reaction. However, the dyspnea still persisted, there was a disproportionate tachycardia and only slight improvement in his responsiveness. On the fifth day the rectal temperature rose secondarily to 102°F., the heart rate continued at 140 beats per minute

and he began to complain of headache. Shortly thereafter he died suddenly, apparently of ventricular asystole, approximately one hundred hours after admission.

**GROSS PATHOLOGY.** *Pleural Cavities:* The left pleural cavity contained 300 cc. of turbid fluid, and the right 200 cc. of similar fluid.

*Pericardial Cavity:* This cavity contained 200 cc. of clear yellow fluid.

*Heart:* The heart weighed 320 Gm. and was somewhat enlarged with dilatation of the right atrium. Situated on the leaflets of the mitral valve were several small verrucae, which were yellow in color and firm in consistency, measuring less than 0.5 mm. in diameter. There was no ulceration of the valve leaflets and the other valves were normal.

*Lungs:* The right lung weighed 640 Gm. There was normal crepitation at the apex. The middle and lower lobes were congested and of firmer consistency. The cut surface of the lower and middle lobes appeared deep reddish-gray and moist, exuding a moderate amount of fluid on pressure. The left lung weighed 590 Gm. The lower lobe was quite congested and when cut presented a red, moist surface which exuded fluid on pressure.

*Liver:* The liver weighed 1,940 Gm. It was of firm consistency and on cut section presented a reddish-brown, slightly granular appearance.

*Kidneys:* The right kidney weighed 180 Gm., the left 190 Gm. External surfaces were smooth, reddish-brown and glistening. Coronal sections revealed numerous small, petechial, hemorrhagic areas throughout the cortex and medulla, measuring less than 1 mm. in diameter.

*Brain and Meninges:* A small amount of purulent exudate covered the cortex and extended to the base.

**MICROSCOPIC PATHOLOGY.** *Heart:* There were scattered areas of old scarring and isolated focal areas of acute myocardial necrosis, with increased vascularity and accompanying collections of polymorphonuclear neutrophils and lymphocytes. A section through the mitral valve showed the pink collagenous tissues of the leaflet; attached to it was a broad-based, papillomatous nodule of lighter staining, fibrous tissue covered by endothelial cells. No colonies of organisms were seen.

*Lungs:* The alveolar spaces in large areas were filled with serum precipitate with very little cellularity. Especially near the lung bases were spotty areas of acute inflammatory reaction involving small bronchioles as well as alveoli. There was pronounced congestion of the pulmonary vessels but no demonstrable thrombi.

*Spleen:* There was marked congestion with the number of polymorphonuclear neutrophils and macrophages also increased. Scattered foci of heavier infiltration with neutrophils occurred.

*Liver:* There was moderate fatty infiltration. Occasional scattered foci of necrosis infiltrated with polymorphonuclear leukocytes predominantly were found.

*Kidneys:* The typical "wire loop" appearance was seen in the glomerular tufts. In addition, there was a varying degree of acute necrosis of other glomerular tufts with accompanying polymorphonuclear infiltration, hemorrhage and fibrin thrombi. Fairly extensive focal interstitial hemorrhages and hemorrhages into the tubules were found. The tubular epithelium of the cortex showed granular swelling and degeneration. There were scattered foci of chronic inflammatory cells, particularly in the cortical areas; frequently there were radial streaks of inflammatory cells along the tubular interstitial tissue. Focal areas of hemorrhagic necrosis were occasionally noted in the cortex, involving groups of tubules, a glomerulus and blood vessels. The latter showed hemorrhage and necrosis of their walls. No bacteria were seen.

*Thyroid Gland:* Numerous areas of acute necrosis with heavy infiltration with neutrophils, lymphocytes and erythrocytes occurred. Some of the blood vessels in these foci were partially occluded by hyaline thrombi; the walls showed slight degenerative change and infiltration with a few red blood cells and polymorphonuclear leukocytes. No organisms were found.

*Skin:* An intradermal vesicle was filled with masses of erythrocytes, a small amount of fibrin, a few polymorphonuclear leukocytes, macrophages and many small clusters of bacteria, mostly bacilli. Another section revealed degeneration and necrosis of the epidermis and adjacent corium, and infiltration with a moderate number of polymorphonuclear leukocytes. The blood vessels were congested but no definite

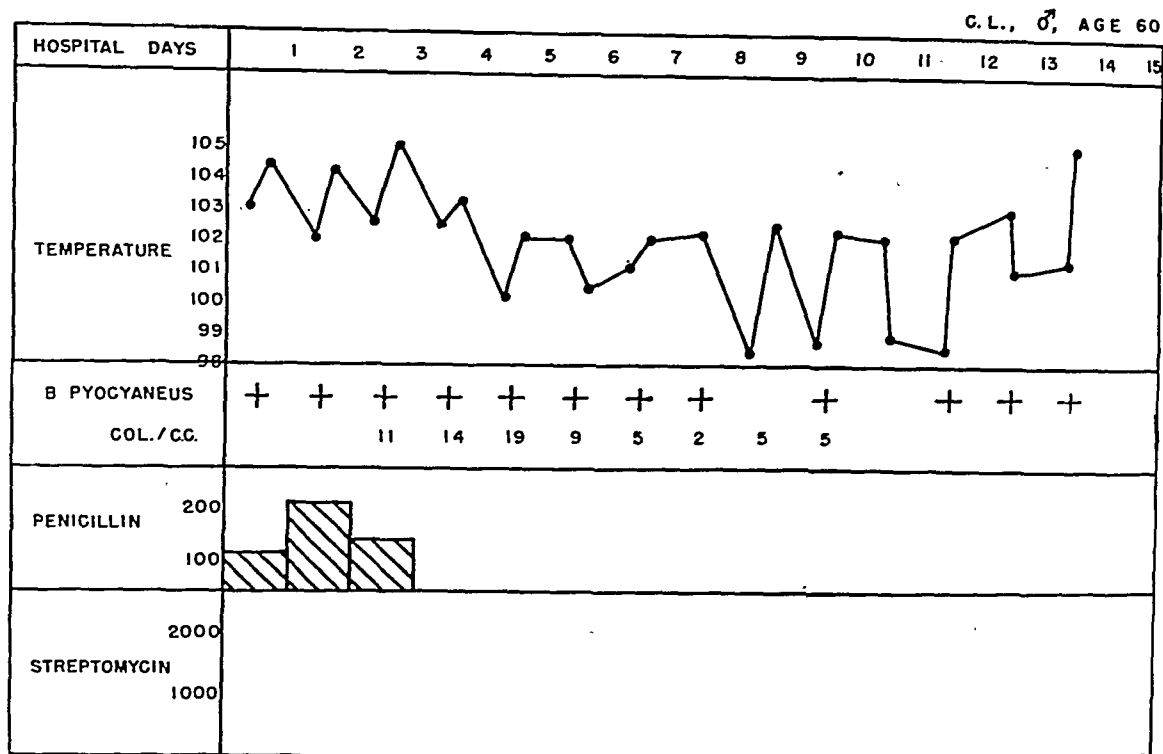


FIG. 3. Case III. Fatal sepsis during chronic lymphatic leukemia, with rapid development of resistance of the organism to streptomycin.

thrombi were found; no bacteria were seen in these areas.

*Sartorius Muscle:* There were numerous hemorrhagic areas in the muscle bundles, which widely separated them. Foci of degeneration and necrosis of the bundles were frequent. Within or near the hemorrhagic lesions were numerous engorged blood vessels with necrotic walls and extravasation of red blood cells and infiltration with polymorphonuclear leukocytes and large mononuclear leukocytes. Some of the smaller vessels were partially or completely occluded with thrombi, composed of masses of fibrin and polymorphonuclear leukocytes. Some of the vessels showed deep blue staining fibrin masses in their walls and deeply staining swollen collagen fibers. Throughout the hemorrhagic areas there was diffuse infiltration with polymorphonuclear leukocytes. No definite bacteria were found.

*Brain:* Sections from the base of the brain and through the cortex showed purulent exudate in the subarachnoid space, consisting of polymorphonuclear leukocytes, macrophages and a few lymphocytes. Occasional gram-negative bacilli were seen in the areas of inflammation.

There were no inflammatory lesions of the nervous tissue.

*Cultures:* From the lungs, heart, blood, etc., there was no growth. Unfortunately, the meningeal exudate was not cultured.

*Final Pathological Diagnoses:* Chronic disseminated lupus erythematosus; *B. pyocyaneus* septicemia with terminal meningitis, and acute and chronic myocarditis with terminal congestive heart failure.

**CASE III.** This was a case of *B. pyocyaneus* septicemia with ulceration of the rectum in a man with chronic lymphatic leukemia. Streptomycin therapy was ineffective because of rapidly developing resistance of the strain of organisms and death followed. (Fig. 3.)

C. L. was a sixty-year-old, white male who was admitted for the first time to the Evans Memorial on October 8, 1945, complaining of weakness and dyspnea on exertion of three weeks' duration, slight anorexia of the same duration, and a weight loss of 10 to 12 pounds during the preceding six months. Following extraction of two teeth two and a-half weeks prior to admission, there was apparently local infection which had not subsided on admission.

Physical examination revealed the patient to be a pale, chronically ill but obese man. Several small ecchymoses were seen on the buccal mucous membrane. There were many flame-shaped hemorrhages in both fundi, with an especially large hemorrhage into the right fovea centralis. The remaining few teeth were carious, loose and there was marked pyorrhea alveolaris present. The spleen was slightly enlarged, being barely palpable. There was no lymphadenopathy.

The urine was normal. There was a marked anemia, the erythrocyte count being 1,770,000 per c. mm. with hematocrit of 19 per cent, hemoglobin 6.2 Gm. per cent, M.C.V. 107 cubic micra, M.C.H. 35 gamma gamma, reticulocytes 2.5 per cent. Total white count was 4,000–8,150 per c. mm. with 8 per cent polymorphonuclear leukocytes, 88 per cent lymphocytes (2 per cent atypical) and 4 per cent monocytes. Thrombocytes were 187,000 per c. mm. Bleeding time averaged eight minutes, clotting time five and a-half minutes. Clot retraction was 49 per cent of plasmatocrit (normal 80 per cent or more). Tourniquet test produced 17 petechiae per square inch (normal less than 15). Sternal puncture revealed the marrow to be infiltrated with lymphocytic elements.

During the first twelve days in the hospital, he received 3,000 cc. of whole blood and 900 cc. of washed red cells. Several febrile reactions occurred, one of which followed extravasation of blood into the left forearm, with swelling, redness and heat. He was treated with penicillin for this, though no etiologic agent was ever demonstrated. He was discharged on the seventeenth day, October 25th, markedly improved, with near-normal blood levels. Diagnosis was chronic lymphocytic leukemia, aleukemic stage, myelophthisic anemia and dental caries with pyorrhea alveolaris.

Thirty-nine days after discharge, he was readmitted (December 3, 1945) with the complaints of recurrent weakness, pain and swelling in the lower jaw and insomnia, all of one week's duration. During the three weeks prior to readmission, he had fourteen teeth extracted in two sittings, which were followed by fever up to 102°F., pain and swelling in the jaws and face and several severe bouts of epistaxis.

Physical examination revealed no essential change except a further weight loss of eight pounds since discharge, complete edentulousness without evidence of infection at the sites of extraction, several small ecchymoses in the skin of the shoulders and arms and a small superficial ulcer at the right base of the tongue.

Laboratory examination showed that there was a severe anemia, with hematocrit of 18 per cent and hemoglobin of 6.1 Gm. per cent. The total white blood count was unchanged, with 7,900 leukocytes per c. mm. 4 per cent polymorphonuclear leukocytes, 95 per cent lymphocytes and 1 per cent monocytes.

In the hospital, multiple transfusions, a total of 2,000 cc. of whole blood and 2,000 cc. of washed resuspended red cells, were given, with an increase in hemoglobin to 10.2 Gm. per cent and in hematocrit to 31 per cent. A small abscess developed on his neck following a cut from a razor; this was treated with local heat and appeared to be healing well when he was discharged on December 12, 1945, nine days after admission.

Five days later, on December 17, 1945, he was readmitted with the complaints of chills, fever and sweats of three days' duration, and an increase in the size and number of the "boils" which he had when he left the hospital. Oral temperature was 103.5°F., pulse 96, respirations 12 per minute, and blood pressure 118/56. He was acutely ill, weak and irritable, but with slightly clouded sensorium. There were many cutaneous petechiae of generalized distribution. Several small superficial abscesses were present on the skin of the neck. At the right submandibular area there was a large (6 by 4 cm.) hot, red, swollen, indurated area in the skin and subcutaneous tissues. A large area of second degree burn (hot water bottle) was present on the skin surrounding the anus and on both buttocks. Exquisite pain was produced by insertion of the finger into the rectum but no ulceration was felt at this time. An anemia similar to that on previous entries was noted with a similar leukocyte count. *B. pyocyaneus* was cultured from the blood daily. This organism, along with others including the hemolytic staphylococcus aureus, was cultured from the blistered areas on the buttocks.

In the hospital, his temperature ranged from 102 to 105°F. during the first three days with a corresponding pulse. Penicillin had been administered pending the blood culture reports; on the second day this was discontinued and streptomycin was begun in the dosages indicated. During the next week, although his temperature was slightly lower, ranging from 100 to 103°F., his general condition grew worse. There was a progressive anemia and leukopenia, for which he was given 2,000 cc. of whole blood. He became incontinent of urine and feces. He was frequently stuporous. Large ecchymoses developed in the skin of his left arm and chest. The abscess in the neck continued unchanged. There was such extreme tenderness in the anal and perineal regions that a digital rectal examination was impossible. He began to cough up small clots of blood frequently. Dyspnea and cyanosis developed which were relieved only partially by oxygen by mask. On December 29, 1945, after nearly ten days of administration, the streptomycin was discontinued. The persistence of the *B. pyocyaneus* bacteria corroborated the insensitivity of the organism to the antibiotic *in vitro*. (Growth of this strain of *B. pyocyaneus* was not inhibited by a concentration of 500 units of streptomycin per cc. of media.) A total of 19,150,000 units of streptomycin was given. On the fourteenth hospital day, there was a rise in temperature to 105°F. He died quietly on December 31, 1945, the same day.

**GROSS PATHOLOGY.** Autopsy was performed eight hours after death. The skin and sclerae were slightly jaundiced. There were numerous petechiae measuring from 0.5 to 1 mm. in diameter over the skin of the back, trunk and extremities. Several larger areas of ecchymosis from 4 to 6 cm. in diameter were present on the arms and legs. In the right superior cervical region were two healing abscesses covered with hard crusts. Healing superficial ulcerations were present in the skin around the anus and over both buttocks.

**Heart:** The heart weighed 420 Gm., was slightly enlarged but was otherwise not abnormal.

**Lungs:** The right lung weighed 725 Gm. The lower one-third was edematous and congested. There were numerous focal areas of hemorrhage, the largest measuring about 2 cm. in diameter.

These were scattered throughout the upper and lower lobes but were more numerous in the lower lobe. The left lung was similar to the right.

**Spleen:** The spleen weighed 250 Gm. and was very soft in consistency.

**Gastrointestinal Tract:** This tract was entirely normal except for the rectum. In the rectum just proximal to the internal sphincter was a large, sloughing ulcer, 7.5 by 7 cm., with a well defined, punched out border and a dirty grayish-green base. The wall of the rectum adjacent to the ulcer was firm and markedly thickened; it measured 1.4 cm. in thickness.

**Kidneys:** The right kidney weighed 280 Gm. At the lower pole large soft adherent thrombi distended the branches of the renal vein. These had the appearance of antemortem thrombi. The left kidney weighed 300 Gm. Antemortem thrombi similar to those seen on the right were observed.

**Bladder:** The mucosa of the bladder was gray and trabeculated and exhibited congestion with several small areas of hemorrhage.

**Bone Marrow:** The femoral marrow was slightly redder than normal. The vertebral marrow was reddish-gray in color and the sternal marrow similar.

**MICROSCOPIC. Rectal Ulcer:** There was extensive degeneration and necrosis throughout the mucosa and submucosa and pronounced infiltration of all coats by lymphoid cells and large mononuclear leukocytes. A fibrino-hemorrhagic membrane covered portions of the necrotic mucosa. The ulceration had extended down through the submucosa and into the muscular coat. In the inner muscular coat there were large areas where the smooth muscle bundles were undergoing degenerative change and were heavily infiltrated with inflammatory cells composed of lymphocytes, plasma cells and large mononuclear leukocytes. There were no polymorphonuclear leukocytes and no definite leukemic cells in the exudate. In the outer muscular coat and serosa there were moderate chronic inflammatory cell infiltration and areas of fibroblastic proliferation. Numerous colonies of bacteria, mostly bacilli, were frequently seen in the necrotic tissue and within engorged blood vessels of the mucosa and submucosa. There was also proliferation of bacilli within the walls

of some of the vessels in the areas of necrosis. In the submucosa there was one large vein which was distended by a recent antemortem thrombus, a portion of which was adherent to the endothelial lining. Beginning fibroblastic organization was noted in one small area. There were colonies of bacteria within the thrombus and within the degenerated vessel walls.

*Lungs:* The blood vessels throughout the lung were markedly congested. A large irregular patchy area of acute bronchitis and bronchopneumonia was found. The exudate in this area was composed chiefly of masses of erythrocytes and fibrin and very few leukocytic cells, these consisting chiefly of lymphoid cells and a few macrophages. There were numerous bacilli in the bronchioles and alveolar spaces.

*Spleen:* There were areas of intense congestion and diffuse hemorrhage. There was a moderate number of large hyperchromatic cells with varying texture and staining reactions which appeared to be lymphoblasts. No foci or erythropoiesis or myelopoiesis were noted. No organisms were seen.

*Bone Marrow:* Focal areas of lymphocytic infiltration mixed with plasma cells and lymphoblasts were present. Cells of the myelopoietic series were very few in number and myelopoiesis is markedly reduced.

*Hemolymph Nodes:* The architecture was well preserved and the capsule was normal. There were occasional large basophilic cells with rare mitoses suggestive of lymphoblasts in the lymph cords and the sinuses.

Changes in the other organs were not striking. In the *kidneys* there was generalized edema, congestion and degenerative changes which accompany benign arteriolar nephrosclerosis. The *prostate* contained an area of infarction. No thrombosed vessels or leukemic infiltrations were seen. In the *liver* congestion and slight edema occurred with slight fatty infiltration and granular disintegration of the cytoplasm of the liver cells.

*Bacteriology:* Specimens taken from the lungs, liver, spleen and bone marrow grew *B. pyocyaneus* in pure culture. Culture of the healing abscess of the skin of the neck showed predominantly hemolytic staphylococcus aureus and a few colonies of *B. pyocyaneus*.

*Final Diagnoses:* (1) Aleukemic lymphatic leukemia; (2) *B. pyocyaneus* sepsis with ulceration of the rectum, and (3) terminal acute bronchitis and hemorrhagic bronchopneumonia.

CASE IV. This patient had undergone multiple operations on the biliary tract. She suffered with wound infections, suppurative cholangitis, liver abscess and repeated bacteremias due to either *B. coli* or *B. pyocyaneus*. Treatment with sulfonamides and streptomycin was not curative, and sudden death occurred during *B. pyocyaneus* bacteremia. (Fig. 4.)

E. D. was a sixty-nine-year-old, white female admitted to the surgical service on January 23, 1946, complaining of right epigastric pain.

In September, 1945, a subtotal thyroidectomy was done for toxic adenomatous goiter, with uneventful recovery and relief of symptoms. There were no other significant illnesses in the past.

Her present illness began with right epigastric pain, sharp and intermittent in character, radiating through to the right scapula, produced by eating fatty or fried foods particularly, about nine months prior to admission. At this time a large, radio-opaque, laminated gallstone was visualized by x-ray. She had never had vomiting, jaundice, bloody or clay-colored stools, chills or fever. Because of persistence of symptoms she entered for operation with a diagnosis of cholelithiasis and chronic cholecystitis.

She was a thin, elderly woman in some discomfort but not severely ill. Temperature, pulse and respiration were normal. There was moderate peripheral arteriosclerosis. There was pronounced tenderness in the right upper quadrant of the abdomen but no other abnormalities. The liver and spleen were not palpable.

On admission, urinalysis was entirely normal. Hemoglobin was 13 Gm. per cent. White blood count was 6,200 per c.mm., with 80 per cent polymorphonuclear forms, 17 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles.

On the second hospital day a cholecystectomy was done. The gallbladder was shrunken and fibrotic and contained a single large stone. At this time what was thought to be a diverticulum of the gallbladder was also removed. Her post-operative course was marked by increasing

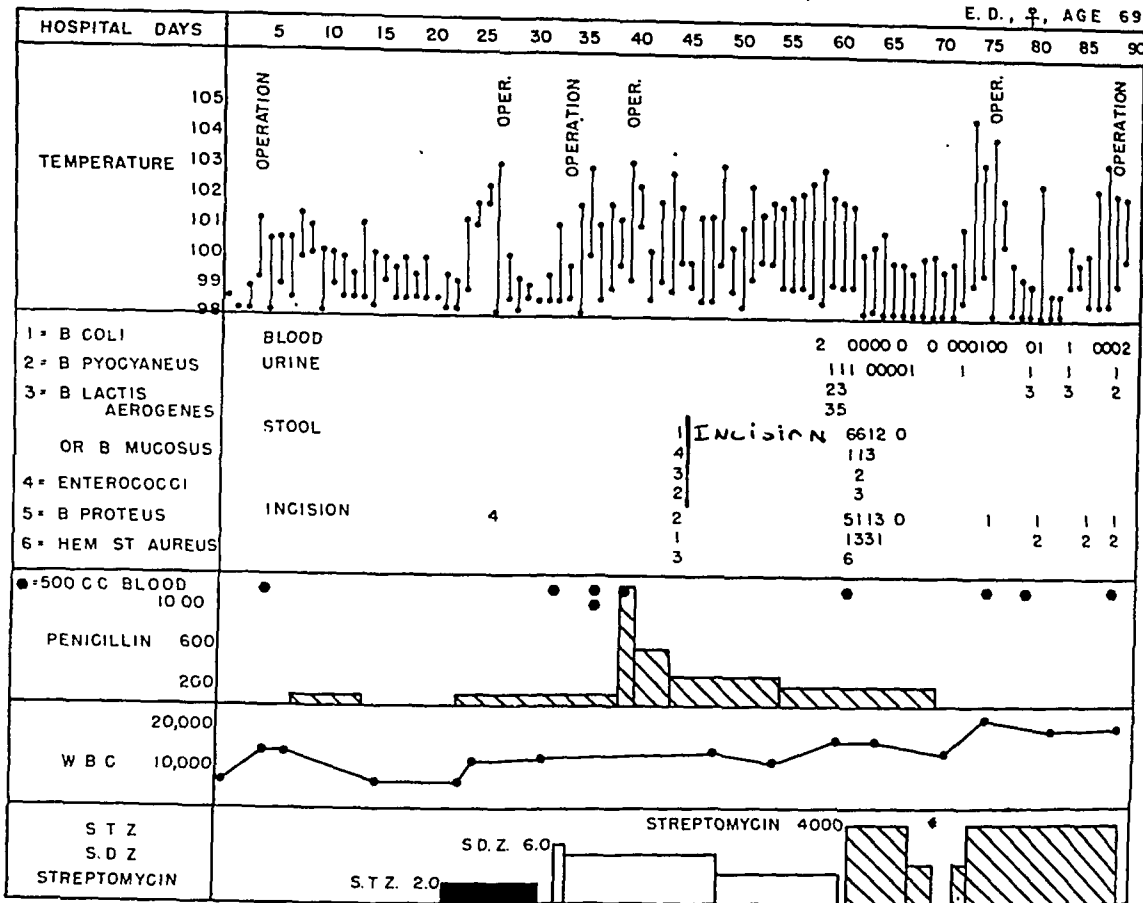


FIG. 4. Case IV. Fatal sepsis (*B. coli* and *B. pyocyaneus*) with suppurative cholangitis and liver abscess following multiple operations on the biliary tract.

icterus. There was a low-grade fever, which, however, rapidly increased to 103°F. from the fifteenth to the eighteenth hospital day. On the seventeenth hospital day, drainage of bile through a sinus in the incision site occurred. At this time exploration of the sinus tract was performed. A moderate amount of purulent bile was found and the area was drained. The temperature returned to normal. However, there was no improvement in the icterus, so on the thirty-third hospital day an exploratory operation was performed, and the common bile duct was anastomosed to the jejunum by means of a vitallium tube. Six days later the abdominal incision was resutured because of partial dehiscence. Although the jaundice diminished satisfactorily, her postoperative course was septic, with chills and daily fever, as high as 102 to 103°F., despite the administration of penicillin and sulfadiazine. Culture of the wound secretions on the forty-eighth hospital day revealed *B. pyocyaneus* predominantly and *B. coli*. On the

fifty-ninth hospital day a blood culture revealed *B. pyocyaneus*. During the next two days cultures of the urine and of the abdominal wounds showed a mixed flora, with *B. coli* and *B. pyocyaneus* predominating. From the sixty-second to seventy-first hospital days, a total of 29 million units of streptomycin was given over a period of nine days in intramuscular injections every three hours. During this time the temperature returned to normal, the urine was sterilized, and the abdominal incisions healed. However, within forty-eight hours after discontinuance of the streptomycin, fever reappeared, with chills associated with a *B. coli* bacteremia on the seventy-fifth day. Streptomycin was begun again on the seventy-fourth hospital day and continued until death, in doses of four million units daily. On the seventy-fifth hospital day, pronounced tenderness developed in the left upper quadrant. There was elevation of the left diaphragm and impairment

of motion. An exploratory incision was made and a small left subphrenic abscess, apparently originating in and communicating with the left lobe of the liver, was drained. *B. coli* in pure culture was grown from the pus. Her temperature diminished rapidly, but soon intermittent chills and fever again appeared, with *B. coli* bacteremia on two occasions during the next thirteen days. Cultures of the urine and of the left upper quadrant incision showed *B. coli* and *B. pyocyaneus*.

Because of continued septic course, with x-ray evidence of elevation of the right diaphragm, an exploration of the right subphrenic region was carried out through a posterior incision on the eighty-ninth hospital day. No evidence of a subphrenic abscess on the right was found. On the afternoon of the ninetieth day she experienced another shaking chill. While the blood was being drawn for culture, she died suddenly. *B. pyocyaneus* was grown from this terminal blood culture.

**GROSS PATHOLOGY.** The body was emaciated. There were no significant skin lesions present. The parietal peritoneum over the right upper quadrant was slate black in color and shaggy. There were many adhesions between the viscera and the anterior abdominal wall, particularly at the incisional sites.

*Spleen:* The spleen weighed 365 Gm. The pulp was very mushy and soft, and the follicles were less prominent than normal.

*Liver:* The liver was normal in size. The choledocho-jejunostomy was patent and functioning, although the area of the liver to which the jejunum was anchored was necrotic and gray in color. On the superior surface and antero-lateral margin of the left lobe there was a ragged cavity 2 cm. deep and 3 cm. in diameter, lined by necrotic tissue and containing thick, gray pus. The abscess was surrounded by adhesions and communicated with the left subcostal incision by a sinus tract. The cut surface of the liver was brownish-yellow and presented a nutmeg appearance. Pinhead-sized and larger drops of yellow purulent material could be expressed from the radicles of the biliary tract.

*Kidneys:* The right kidney weighed 170 Gm. and the left 160 Gm. On cut surface the pallor was marked. The cortices were 3 mm. thick. The

capsules stripped easily and revealed finely granular surfaces. The left pelvis and ureter were normal. There was a double pelvis and ureter on the right. The pelvis and ureters of the right kidney were slightly injected and contained yellow pus. The perirenal fat on the right was thickened and edematous.

*Urinary Bladder and Urethra:* The mucosa of the urinary bladder and urethra was markedly hemorrhagic and edematous. The vesicle contained thick, yellow pus.

*Gastrointestinal Tract Pancreas and Adrenals:* These organs were normal.

*Heart:* The heart was normal except for a moderate degree of atheromatosis of the coronary arteries.

*Lungs:* The lungs were normal except for complete atelectasis of the lower half of the right lower lobe. There were no infarcts, antemortem thrombi or emboli.

*Trachea and Bronchi:* The trachea and bronchi were essentially normal. There were no antemortem thrombi discovered after complete dissection of the tributaries of the inferior vena cava.

**MICROSCOPIC PATHOLOGY.** *Liver:* There was patchy disorganization of the lobules with intervening fairly normal areas. In the latter the liver cords were widely separated by markedly dilated sinuses packed with red blood cells. The lumens of some of the bile ducts were filled with polymorphonuclear leukocytes, and there was an increase in the periportal connective tissue. In some areas necrosis of the lobules had occurred with fibrous replacement; the connective tissue contained scattered lymphocytes and an occasional necrotic liver cell. One section through the main intrahepatic ducts showed necrosis of the liver lobules and tremendous periductal fibrosis with lymphocytic infiltration. The epithelium of the ducts was completely desquamated. The wall of the abscess in the left lobe consisted of fibrin, polymorphonuclear leukocytes, large mononuclear leukocytes and a few necrotic liver cells. This fibrino-purulent exudate contained several small scattered groups of bacilli. The liver capsule in this area was thickened, fibrotic and infiltrated with lymphocytes, large mononuclear leukocytes and a few polymorphonuclear leukocytes.



*Spleen:* There was some hyalinization of the walls of the arterioles. The sinuses were engorged with red blood cells, polymorphonuclear leukocytes and a few large mononuclear leukocytes. In one section there was marked congestion of the pulp with diffuse hemorrhage and intensive polymorphonuclear infiltration. No organisms were seen.

*Kidneys:* There was a patchy distribution of inflammatory and degenerative changes. Beneath the capsule roughly triangular areas of lymphocytic infiltration occurred. There was hyalinization of the basement membrane of the glomeruli near these areas; some glomeruli were completely hyalinized. In some glomeruli a few scattered polymorphonuclear leukocytes were found. The capsular spaces contained deposits of granular material. The convoluted tubules were lined by deeply eosinophilic staining cells, some of which were vacuolated and some were desquamated. Most of the tubules contained albuminous deposits and a few desquamated epithelial cells. In the lumens of the collecting tubules were basophilic staining casts. The blood vessels were thickened and showed intimal fibrosis with occasional reduplication of the internal elastic lamina. No organisms were seen.

*Bladder:* In some areas the epithelium of the mucosa was desquamated. There was marked edema of the submucosa. The cells were widely separated and heavily infiltrated by lymphocytes, plasma cells and large mononuclear leukocytes. There were numerous hugely dilated, engorged, thin-walled blood vessels in the submucosa.

*Lungs:* The pleura was thickened and fibrotic with numerous foci of lymphocytes and large mononuclear leukocytes. There was intimal fibrosis of the blood vessels in the fibrotic areas.

The other organs were not significantly abnormal, except for slight atherosclerosis of the coronary arteries and the aorta. No vascular lesions characteristic of *B. pyocyaneus* septicemia could be found.

Cultures from the peritoneal cavity near the hilum of the liver showed *B. coli*, *B. pyocyaneus*. Cultures from the liver revealed *B. coli*, *B. pyocyaneus*, *B. mucosus capsulatus*, and cultures from the spleen showed no growth.

*Final Pathological Diagnoses:* Acute and chronic suppurative cholangitis—*B. coli* and *B. pyo-*

*cyaneus*; liver abscess with sinus to anterior abdominal wall—*B. coli* originally; secondarily infected with *B. pyocyaneus*; biliary cirrhosis (infectious) slight; localized peritonitis with adhesions—*B. coli* and *B. pyocyaneus*; chronic pyelonephritis; chronic cystitis; pulmonary atelectasis, right lower lobe, and coronary and aortic atherosclerosis, slight.

#### INVOLVEMENT OF THE SKIN AND APPENDAGES

The skin is the most frequently involved organ in local as well as systemic infections.<sup>2</sup> This would be expected from the common location of the organisms in moist areas of the normal skin in the axillary and anovulval regions particularly in people who bathe infrequently.

*Local Infections.* In its rôle as an ubiquitous secondary invader *B. pyocyaneus* often contaminates surgical wounds especially those in the abdomen and perineum. Its presence can be recognized by the characteristic blue-green pus produced. The organism was first isolated in pure culture by Gessard<sup>1</sup> in 1882 from such situations. Slowly healing indolent ulcers such as varicose and thrombophlebitic ulcers and chronically draining sinuses from tuberculous and pyogenic osteomyelitic foci are commonly secondarily infected with the *B. pyocyaneus*. Invasion of untreated decubitus ulcers in the sacral region almost always occurs (Case 1).

Mallannah<sup>30</sup> reported the case of an Indian with several perforating ulcers of the foot which with several other features so resembled leprosy that specific treatment had been given, but without benefit. No lepra bacilli were identifiable in the scrapings, but there were many gram-negative bacilli which proved to be *B. pyocyaneus* on culture. The duration of the illness was one year; recovery occurred after treatment with autogenous vaccine for eight weeks.

Kopetzky and Almour<sup>31</sup> described five cases of an erysipelas-like cellulitis of the

skin which spread from mastoid wounds. In one case the mastoiditis was apparently primarily due to this organism while in the others the wounds were secondarily infected after operation. No hemolytic streptococci were culturable from the wounds at the time of the spreading skin infection. The cellulitis involved the scalp, face and neck, and in one instance gangrene of the subcutaneous tissue of both eyelids was produced.

Goldman and Fox<sup>32</sup> described two cases of infection of the skin surrounding the fingernails with development of a brilliant green discoloration of the nails which persisted after subsidence of the paronychia. The soluble green pigment had apparently penetrated the nails without actual infection of the latter.

*Cutaneous Manifestations of Systemic Infections.* Prominent among the signs of pyocyaneus sepsis are skin lesions which begin as macules or vesicles and later become bullous and often pustular. When the surface epithelium is denuded from these latter and the center sloughs out a characteristic ulcerating gangrenous lesion is produced. This was first described by Barker<sup>34</sup> in 1897 and was later called "ecthyma gangrenosum" by Hitschmann and Kreibich.<sup>25</sup> Detailed descriptions of ecthyma of this type were given by Fraenkel<sup>2</sup> in his classic paper in 1917. It is most commonly encountered in the ano-genital region, also in the axillae, inner aspects of the thighs and the abdomen, particularly in children. The organism is easily cultured in abundance from these areas of gangrenous skin. The necrosis may penetrate through the skin and subcutaneous tissue to the underlying muscle. Fraenkel considered that the pathognomonic histologic picture was the finding of thick collections of slender gram-negative rods in the vessel walls of a lesion, particularly in the media and adventitial layers. Sometimes there was a panarteritis with arterial thrombosis. The

pathogenesis of such lesions is apparently the result of two factors, actual cutaneous infarction through mechanical plugging of the vessels because of multiplication of bacilli in their walls, as well as the action of a proteolytic enzyme produced locally by the large numbers of organisms.

Other lesions of the skin seen during the course of bacteremia include the roseola which resembled rose spots occurring in cases of "Shanghai fever" described by Dold.<sup>15,16</sup> This entity closely simulated typhoid fever except for its short duration. *B. pyocyaneus* could be cultured from the cutaneous lesions, but they spontaneously involuted and never progressed to ecthyma.

The report of Guy and Cohen<sup>33</sup> concerns the development of typical generalized exfoliative dermatitis of the newborn (Ritter's disease) in a premature infant. At autopsy on the ninth day was found acute pericarditis, pleuritis and peritonitis all due to *B. pyocyaneus*, and shallow ulcers throughout the small intestine. *B. pyocyaneus* was also cultured from the heart blood. It is quite likely that the sepsis in this baby had its origin in infection of the umbilicus.

Erythema nodosum,<sup>35,36</sup> erythema multiforme and butterfly lesions of the face<sup>26</sup> resembling lupus erythematosus have also been described during the course of systemic infections with *B. pyocyaneus*. The relationship of these manifestations to the disease is not clear as no cultures or microscopic examinations were carried out.

#### INVOLVEMENT OF THE GASTROINTESTINAL TRACT

Next to the skin the alimentary tract is the most frequently invaded part of the body. Any portion may be involved from the lips, mouth and pharynx to the rectum and anus.<sup>2,23,26,34,37</sup> There is now adequate evidence<sup>37</sup> that the lesions of the stomach and intestines at least can be either primary,

resulting from local invasion from organisms in the lumen, or secondary to bacteremia and hence analogous to the skin lesions *ecthyma gangrenosum*.

In general, the pathologic lesions consist of circumscribed 2 to 12 mm. areas of necrosis of the surface epithelium which appear grossly as ulcers with the bases covered with yellow crusts. In the tonsil the necrosis may produce deep cavities which extend to include the capsule and even penetrate into the surrounding muscle.<sup>2,37</sup> In the ileum the ulcerations involve not only the Peyer's patches but also the adjacent mucosa and usually lie opposite the attachment of the mesentery.<sup>37</sup> Confluence of these ulcerations may result in the involvement of large areas of the small intestine<sup>34</sup> or the stomach.<sup>2</sup> On section extension into the submucosal layer is often seen. Large masses of bacilli are found in the necrotic bases and margins of the ulcers (Cases I and III). The blood vessels in the periphery of the lesions are often thrombosed and characteristically show infiltration with large numbers of organisms especially in the media and adventitia and in the perivascular spaces. Suppurative mesenteric adenitis with a pure culture of *B. pyocyaneus* from the involved glands was described by Barker,<sup>34</sup> although this is rare; hyperemia without other change is the usual finding. Gangrene of the anorectal region with extension into the ischio-rectal fossa and involvement of the overlying skin has been noted.<sup>26</sup>

The clinical picture varies considerably. Infants and young children<sup>2,38,39</sup> are specially apt to be afflicted. On the lips and soft palate the lesions may be punctate and resemble "aphthous" ulcers. At the other extreme the necrosis of the tonsil and pharyngeal mucous membrane may be so great as to simulate severe scarlet fever or diphtheria.<sup>2,23,24,27</sup>

Epidemics of diarrhea of the newborn with high mortality have been ascribed to

this agent. In children and adults an acute or subacute enteritis with diarrhea alternating with constipation and with or without significant constitutional symptoms may occur.<sup>2,38,39,40</sup> However, on occasion the disease may assume the picture of typhoid fever<sup>15,16</sup> with prostration, headache, high fever, roseola from which the organisms can be recovered, splenomegaly and bacteremia in addition to the gastrointestinal manifestations. Some of these cases have been characterized by Dold as "Shanghai fever" or "13-day fever" because of their short duration. This similarity to typhoid is heightened by the frequent finding of *B. pyocyaneus* in the bile and in the gallbladder at autopsy and operation, and in experimental animals with induced bacteremia.<sup>35,37</sup> None of the catastrophic complications of typhoid, as massive hemorrhage into the gastrointestinal tract or perforation of the gut with peritonitis, has been reported, although the case of peritonitis<sup>34</sup> is suggestive.

The diarrheal stools have been noted to be greenish, mixed with mucus and blood-streaked. There is no mention of purulent stools in the literature. Culture may yield a striking abundance of *B. pyocyaneus*; at times as high as 50 to 75 per cent of the colonies are those of this organism.

In this connection, it may be noted that the finding of *B. pyocyaneus* in routine stool cultures is not common and the number of organisms is small; positive cultures vary from 13 out of 3,000<sup>12</sup> to 2.5 per cent of 124.<sup>11</sup> In the latter group the cultures were made in an area where contamination of the drinking water with this organism was frequent.

In diagnosis obviously reliance must be placed mainly on recovery of the organisms from the local lesions, stools or blood. If *ecthyma gangrenosum* is present, additional strong evidence is adduced as to the causative rôle of the *B. pyocyaneus*. A rising titer

of agglutinins against the patient's own organism may afford further necessary evidence when the only bacteriologic finding in a case of enteritis is a positive stool culture.

#### INFECTIONS OF THE URINARY TRACT

In the overwhelming majority of instances the finding of *B. pyocyaneus* in the urine together with other evidences of infection indicates that there has been previous manipulation, either catheterization, cystoscopy, or bladder or kidney surgery, with introduction of the organisms in this manner.<sup>42,47</sup> The frequent presence of the organism on the skin of the ano-genital region is a factor which makes such implantation relatively easy especially in females. These infections are frequently mixed, with several varieties of gram-negative bacilli in the urine, usually including *B. coli*.

In adults one of the commonest portals of entry of this organism is by way of the urinary tract. Bacteremia is the common cause of "catheter chills"; occasionally *B. pyocyaneus* is the organism cultured from the blood (four of eighty-two patients with positive blood cultures—Scott;<sup>42</sup> one of sixty-four patients with positive blood cultures—Hyman and Edelman.<sup>43</sup> Other instances of bacteremia following instrumentation have been reported by Barrington and Wright<sup>44</sup> and by Ewell<sup>45</sup> and with secondary localization elsewhere by Scheim<sup>110</sup> (thoracic vertebrae), Moragues and Anderson,<sup>50</sup> Fish et al.<sup>48</sup> (endocarditis) and Kline and Maschke<sup>26</sup> (lung).

Most frequently in ascending infection cystitis alone is produced. When involvement of the bladder mucosa is superficial, with hyperemia and edema only as is usually the case, the prognosis is relatively good though bacilluria may persist for some weeks and recur following cessation of therapy. Obviously other factors such as

obstruction with presence of residual urine may be more important here than the type of infecting organism. On rare occasions the mucosal lesions may assume a necrotic character similar to those encountered in involvement of the gastrointestinal tract.<sup>34</sup> Our Case 1 is an extreme example of this type of cystitis, with extension of the necrosis of the mucous membrane to the ureter and kidney pelvis.

Prostatitis with abscess formation has been described twice.<sup>48,50</sup> Curiously enough dissemination from these foci resulted in endocarditis in both cases. There was thrombosis of the periprostatic veins in one case.

Extension to the kidney with abscess formation throughout is rare and appears to present a histological picture similar to ascending pyelonephritis of equal severity caused by other organisms such as *B. coli* (Case 1).<sup>46,26</sup> In Fraenkel's case,<sup>2</sup> however, the cellular infiltration of the lesions was almost entirely mononuclear, in contrast to the predominantly polymorphonuclear character of the exudate described by Kline and Maschke and Roedelius, and in our case.

In contrast to the picture in ascending pyelonephritis is that seen in the kidney in sepsis.<sup>2,46</sup> During the latter the tendency to vascular inflammation is commonly manifested in the kidney with infiltration of arteriolar and arterial walls with bacilli, thrombus formation and production of infarcts. These areas of anemic necrosis do not break down and suppurate. Areas of focal glomerulonephritis have been noted in only one case, that of a patient with acute endocarditis.<sup>50</sup>

*B. pyocyaneus* does not split urea to form ammonia. No tendency to stone formation is associated with *B. pyocyaneus* urinary tract infection. Only one report concerns this subject:<sup>46</sup> Following removal of an aseptic calcium oxalate stone from the

kidney pelvis a unilateral pyelonephritis developed which was refractory to treatment. One year after the first operation the kidney was removed after formation of a second stone, this time composed of calcium phosphate; from the center of this calculus *B. pyocyaneus* was cultured.

**CASE V.** In this case there was benign prostatic hypertrophy with bladder neck obstruction and cystitis and pyelonephritis due to *B. coli*, *B. pyocyaneus* and *B. mucosus*. Infection by all organisms persisted following operation and treatment with sulfathiazole (penicillin) and streptomycin.

E. H. was a sixty-four-year-old male who complained of frequency and nocturia. During the two years before admission, there was a progressive decrease in the size of the urinary stream, nocturia two times per night and day frequency. During the week before admission, there was diarrhea with slight fever, lower abdominal cramps and partial urinary retention with constant dribbling.

The temperature was normal and the chest was emphysematous. There were bilateral large direct inguinal hernias. The bladder was distended half-way to the umbilicus. No costovertebral angle tenderness was present. There was three plus prostatic enlargement with a nodule in the left lobe.

Laboratory examination revealed the following: Urine: Specific gravity 1.024; no albumin or sugar; and many leukocytes and erythrocytes in the sediment. Culture revealed *B. coli*, *B. pyocyaneus* and *B. mucosus*, 95,200,000 per cc. before streptomycin was started. Non-protein nitrogen was 43 mg. per cent. Intravenous pyclogram: Both kidneys were normal in size, shape and position. There was a minimal degree of dilatation of the renal pelves and calyces of both kidneys, more marked on the right. The pelvic portions of both ureters were dilated and remained filled. There was trabeculation of the bladder. The base of the bladder was elevated due to prostatic enlargement.

After four days of sulfathiazole therapy (1.5 Gm. daily) at the hospital a suprapubic prostatectomy was performed. During the fifteen days after operation there was a low-grade fever,

as high as 100.6°F. Sulfathiazole was continued and penicillin, 120,000 units per day, was given. On the twenty-second hospital day, after the above findings indicated a persistent infection, penicillin and sulfathiazole were discontinued, and streptomycin, 1 Gm. daily, was administered for a total of 9.5 Gm. The streptomycin likewise failed to sterilize the urine, but the slightly elevated temperature returned to normal during its administration, where it remained during the remainder of the hospital course.

**CASE VI.** In this case bladder calculus with cystitis and left pyelonephritis due to *B. pyocyaneus*, *B. coli*, *B. proteus* and *B. mucosus* were present. After operation and streptomycin treatment all organisms were eliminated from the urine except *B. coli*, which persisted in increased numbers.

N. S. was a seventy-two-year-old male whose chief complaints were suprapubic and low back pain and dysuria. Following suprapubic prostatectomy several years ago for benign prostatic hypertrophy, he had been asymptomatic. Five months before admission pain on urination in the perineal and suprapubic regions, low backache and nocturia five to six times a night had begun and continued until admission. X-ray examination revealed a bladder stone.

His temperature was normal and blood pressure was 140/60. There was generalized arteriosclerosis of a moderate degree and a right direct inguinal hernia. There was moderate tenderness in the left costovertebral angle and flank. The prostate was firm, slightly enlarged symmetrically and slightly tender.

Laboratory examination revealed the following: Urine: albumin 2+; sugar negative. Microscopic examination: many leukocytes and erythrocytes in the uncentrifuged specimen. Non-protein nitrogen was 41 mg. per cent. Hemogram was normal. Urine culture before treatment revealed *B. pyocyaneus*, *B. coli*, *B. proteus* and *B. mucosus*, 28,000,000 per cc.

On the third hospital day, a suprapubic cystotomy and removal of the calculus was performed. On the day following operation, streptomycin, 0.25 Gm. every six hours intramuscularly (1 Gm. daily), was begun and continued for a total of 5.75 Gm. The urine was sterilized of the other organisms except *B. coli*, which was pres-

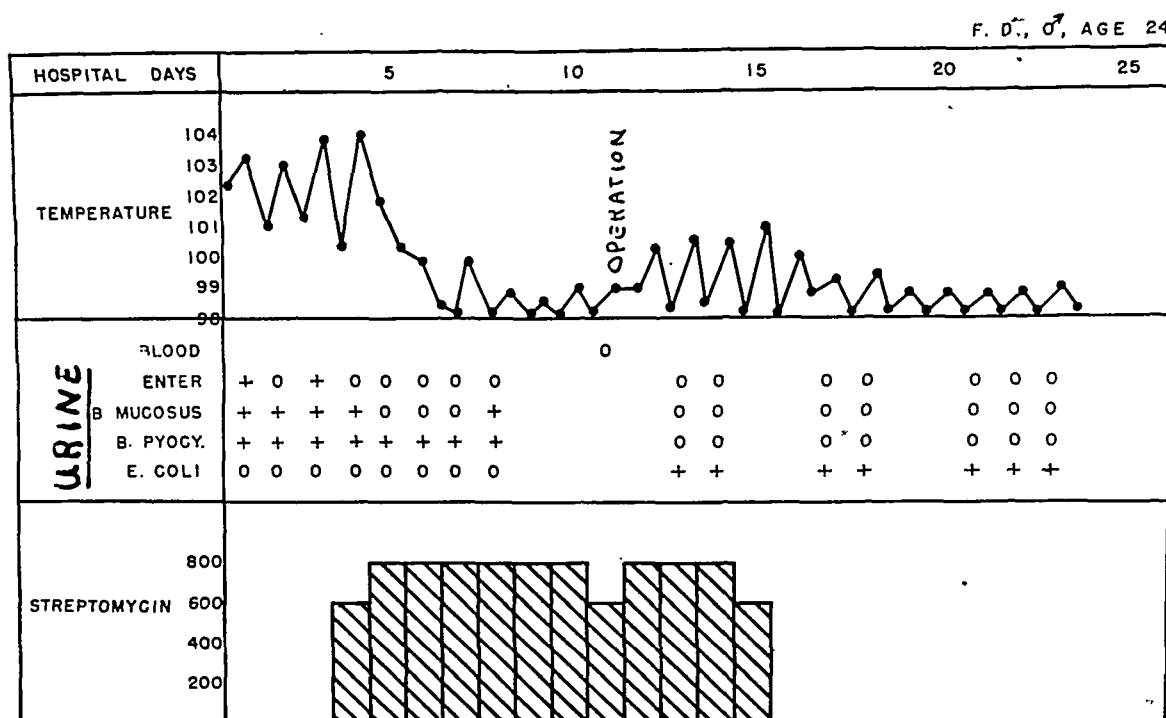


FIG. 5. Case VIII. Development of persistent bacilluria due to a different, resistant organism after operation and streptomycin treatment had apparently cured a mixed urinary infection.

ent in increased numbers (148,000,000 per cc.) on discharge.

CASE VII. Benign prostatic hypertrophy with bladder neck obstruction and cystitis were present due to *B. coli*, *B. pyocyaneus*, and *B. mucosus*. Operation and treatment with streptomycin were carried out followed by sterilization of the urine of the latter two organisms but persistence of the *B. coli* infection.

J. L. was a sixty-seven-year-old male whose chief complaint was nocturia and dysuria of three years' duration. For the fifteen years before admission slight urinary frequency and nocturia had been present and had gradually progressed. On admission there was nocturia five to six times, with slight pain at the beginning of urination, difficulty in starting urination, small stream and terminal dribbling. There had been no retention.

Upon admission his temperature was 98.6°F. The only significant abnormal finding was a prostate which was enlarged to two times normal size but non-nodular and symmetrical.

Laboratory examination revealed the following: Urine: albumin, slightest possible trace; sugar, negative; occasional leukocytes, no erythrocytes or casts. Urine culture: *B. coli*, *B.*

*mucosus*, and *B. pyocyaneus*. Blood: normal. Non-protein nitrogen 36 mg. per cent.

On the fourth hospital day, a transurethral prostatectomy was performed following which streptomycin, 0.25 Gm. every six hours intramuscularly, was started. An uneventful post-operative course ensued except for a febrile rise on the fourth day after operation which may have been due to the removal of the Foley catheter or to the streptomycin. The streptomycin was discontinued on the fourth day; following this, the temperature promptly returned to normal. During the course of therapy, the *B. pyocyaneus* and *B. mucosus* disappeared from the urine, although *B. coli* was still present on discharge on the eleventh hospital day.

CASE VIII. Mixed urinary infection due to *B. pyocyaneus*, enterococcus and *B. mucosus* developed after instrumentation in a patient with renal lithiasis. These organisms disappeared after treatment with streptomycin and nephrectomy, but a strain of *B. coli* appeared then which resisted further therapy. (Fig. 5.)

F. D. was a twenty-four-year-old male who had been discharged from this hospital three days before after studies, including cystoscopy and retrograde pyelography, had revealed a

large stone in the left kidney. Nephrectomy had been advised. During the intervening three days he had had fever, ranging between 101 and 103°F., malaise, vomiting and passage of mucus and pus in the urine. There had been no back pain or chills. He had been given 2 Gm. of sulfa drug and 30,000 units of penicillin during the twelve hours before entry.

Physical examination revealed the temperature to be 102°F. The only other significant findings were slight dehydration and slight bilateral costovertebral angle tenderness. The prostate was normal.

The hemogram was normal, with white blood count 6,550 per c. mm. Non-protein nitrogen was 23 mg. per cent. Urine cultures before treatment showed *B. pyocyaneus*, enterococci and *B. mucosus*. After treatment and operation, these organisms disappeared but *B. coli* appeared and persisted in the urine until discharge.

The patient's temperature remained elevated, 101 to 103°F., during the first five hospital days, but fell rapidly to normal after institution of streptomycin therapy, 0.2 Gm. intramuscularly every six hours, on the fourth day. This was continued for eleven days, including four days after operation, for a total of 9 Gm. On the eleventh hospital day a left nephrectomy was performed. The course following operation was uneventful, there being a low-grade fever, as high as 101°F., during the first five postoperative days. He was discharged with the persistent *B. coli* bacilluria to be further treated as an out-patient.

#### ENDOCARDITIS

Endocarditis due to the *Bacillus pyocyaneus* is one of the rarest manifestations of infection with this organism. The literature was reviewed by Fish, Hand and Keim<sup>48</sup> in 1937 at which time a case of their own was added. Since that time Kearns<sup>49</sup> and Moragues and Anderson<sup>50</sup> have reported cases. This brings the total number of previously reported cases to eight, at least one<sup>51</sup> of which is of doubtful validity. Because of their rarity the cases described in the literature are summarized briefly below.

To this total we add a somewhat unusual case (Case ix).

Barker<sup>34</sup> (1897) reported the first case, that of a forty-one-year-old woman who had had diarrhea, vomiting and anorexia, asthenia and swelling of the right leg of three or four weeks' duration. The patient was pale and emaciated with tense protuberant abdomen, saphenous thrombophlebitis and beginning sacral decubitus. At autopsy on the seventh day a vegetative mitral endocarditis, extensive ulceration of the small and large intestine with acute peritonitis, chronic pelvic cellulitis, peritonitis with ovarian abscess and a recto-vaginal fistula were found. There were also cancer of the stomach, old pulmonary tuberculosis, acute and chronic bronchitis with bronchiectasis and fibrino-purulent pleurisy and a double hydronephrosis with amyloid disease of the kidneys. Cultures from the mitral vegetations, peritoneum, intestinal ulcers, and ovarian abscesses showed pure growths of *B. pyocyaneus*. The portal of entry here apparently was the gastrointestinal tract. (This is the same case reported by Thayer<sup>52</sup> in 1926.)

Blum's<sup>53</sup> case (1899) was that of a baby boy two and one-half months old who also had congenital syphilis. It is not known by which route the organism gained entry to the blood stream. There was no apparent focus of infection; there were no blood cultures taken during life. At autopsy endocarditis of the mitral valve was found; many gram-negative bacilli were seen in the vegetations which proved to be *B. pyocyaneus* in pure culture.

De la Camp<sup>54</sup> (1904) described a fifty-one-year-old woman with a chronic illness of over a year's duration characterized by daily chills, fever, severe headache and numerous cutaneous abscesses which appeared intermittently during the course. On admission she was thin, icteric, had hepatomegaly and tremendous splenome-

galy. The heart was apparently normal. During the thirty-eight-day hospital course it was demonstrated that abscesses of the skin and external ear contained *B. pyocyaneus*. Vesicular and bullous skin lesions and others characteristic of ecthyma gangrenosum also appeared. At autopsy there were five warty, hard, light grey-red, firmly adherent vegetations on the free margins of the mitral valve. Also present were caries of the right petrous bone, recent infarcts of the spleen, saccular aneurysm of the splenic artery (? mycotic) and ulcerations of the nasal mucous membrane. *B. pyocyaneus* was cultured from the heart's blood in pure culture and with staphylococcus from the scrapings of the mitral vegetations and from the spleen. The portal of entry was probably the skin, although this is not definite. *B. pyocyaneus* was not recovered from the blood during life.

Rolly<sup>55</sup> (1906) reported a case of a twenty-eight-year-old woman who died after an illness of eleven days' duration. Two months before her fatal illness she had had a period of fever and abdominal pain from which, however, she recovered in ten days. She was treated for typhoid fever because she was living in a house where there were several other cases of typhoid, although there were no typical manifestations of the disease in the patient and a prompt recovery was made. Her course was characterized by septic temperature, many hemorrhagic skin emboli, splenomegaly and meningitis with terminal bronchopneumonia. *B. pyocyaneus* was repeatedly demonstrated in the blood and in the spinal fluid. At autopsy there was found to be purulent meningitis, vegetative endocarditis implanted on an old mitral valvular lesion, metastatic abscesses in the spleen and kidneys, enlarged uterus with partially retained placenta, corpus luteum of pregnancy and confluent lobular pneumonia. *B. pyocyaneus* was grown from the blood, meninges,

mitral vegetations and various other organs. It was thought that the source of entry of the organism was the uterus.

Kearns'<sup>44</sup> (1936) case was that of a thirty-five-year-old heroin addict who complained of anorexia, weakness, fever, chilly sensations and painful swelling of the left forearm. On admission there was a temperature of 102°F., bilateral bronchopneumonia and an abscess on the dorsum of the left forearm. During a febrile downhill course of eighteen days' duration repeated cultures of his blood and urine yielded *B. pyocyaneus* alone. Postmortem revealed endocarditis of both the aortic and mitral valves and bilateral bronchopneumonia. The intima of the aorta in one location adjacent to the aortic valve was necrotic. There was focal endarteritis of the pulmonary artery a short distance above the pulmonic valve. Numerous slender bacilli in groups and short chains were demonstrated in all these lesions. No postmortem cultures were reported. The portal of entry was the skin abscess.

Fish, Hand and Keim<sup>48</sup> (1937) described a case of a seventy-one-year-old man with recurrent acute urinary retention which had necessitated repeated catheterizations. A suprapubic prostatectomy was done for benign prostatic hypertrophy. Sections of the excised prostate revealed focal suppurative prostatitis with abscesses. Later, on retrospective search, gram-negative bacilli were found in clusters around remnants of corpora amylacea in these abscesses. Between the seventh and twenty-seventh post-operative days there was a septic course, with six blood cultures positive for *B. pyocyaneus* during the last eight days. At autopsy on the twenty-seventh day post-operatively there was vegetative endocarditis of the aortic valve with the underlying valve necrotic and infiltrated with polymorphonuclear leukocytes. Within the vegetation were many colonies of gram-negative bacilli.



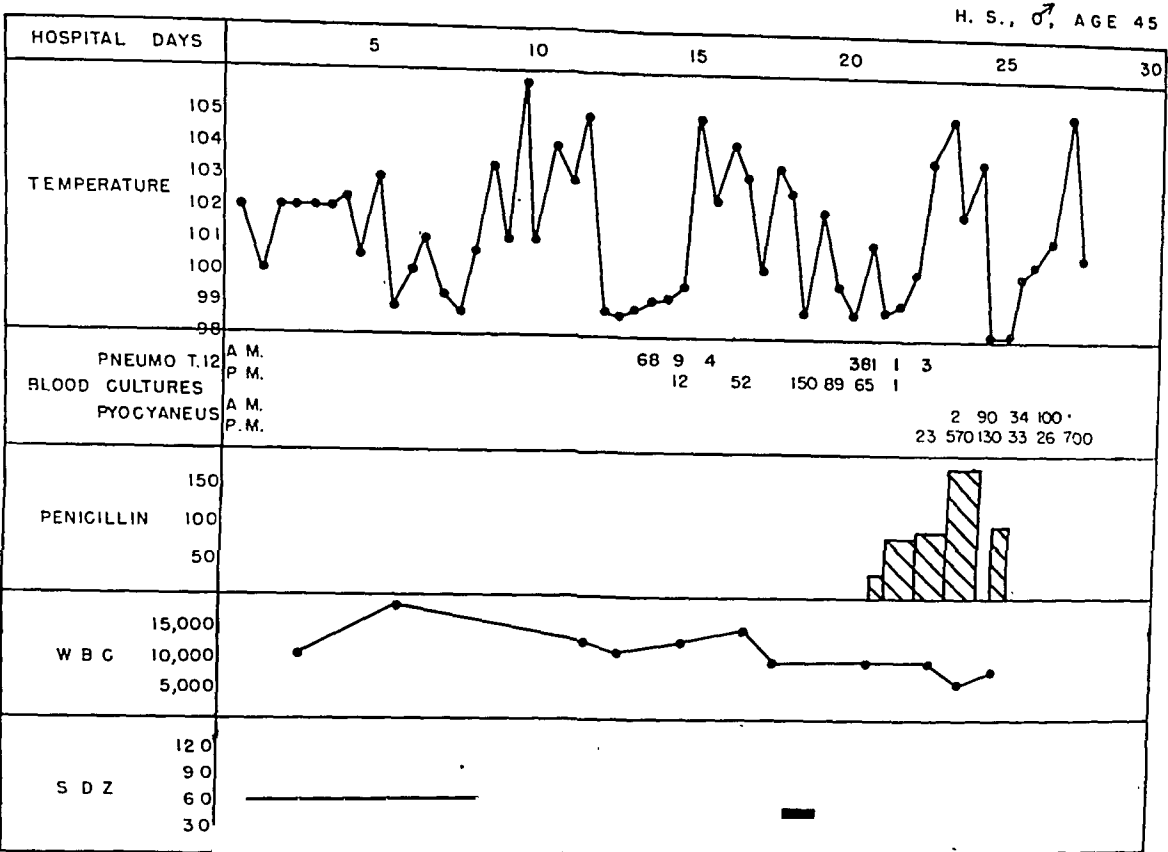


FIG. 6. Case IX. Pneumococcus endocarditis cured by penicillin treatment with death caused by superimposed pyocyaneus endocarditis.

In the aorta above the valve there were two large granular areas of acute bacterial aortitis with similar organism found in their interiors. There were focal necroses in the liver and kidneys. A branch of the renal artery was thrombosed and the wall infiltrated with polymorphonuclear leukocytes. The focus of infection was the prostate with inadvertent dissemination at the time of operation.

Moragues and Anderson<sup>50</sup> (1943) described a sixty-six-year-old diabetic man who had had symptoms of urinary obstruction for three months, dyspnea for two weeks and high fever, chills, headache and diarrhea for four days before admission. During his fifteen-day hospital course his temperature was septic and there were three blood cultures positive for *B. pyocyaneus*. On the ninth day he developed meningitis, with pleocytosis of the spinal fluid (567 cells per

c. mm.) but with the fluid sterile on culture. At necropsy there was mitral stenosis with large friable grayish vegetations on the auricular surface of the valve. There was an abundance of small rod-shaped bacteria in the mitral vegetations which were identified culturally as *B. pyocyaneus*. This organism was also cultured from the meninges. There was infiltration of the meningeal blood vessels by acute inflammatory cells. There were areas of necrosis with abscess formation in the prostate, with bacteria demonstrable in these abscesses. There were areas of infarction and acute focal glomerular nephritis in the kidneys.

Bungeler<sup>51</sup> (1927) described the case of a sixty-five-year-old man who had rheumatic heart disease with mitral insufficiency and who died from sepsis following repeated intravenous injections of a mixture of live organisms among which were *B. pyocyaneus*

("saprovitin"). At necropsy endocarditis of the mitral valve with perforation was found, with multiple small abscesses in the kidneys and spleen. Postmortem blood culture from the femoral vein was sterile. From the spleen, *B. proteus*, *B. pyocyaneus* and cocci in chains were grown. There were no blood cultures taken during life, no cultures from the heart valves and no descriptions of microscopic sections of the vegetations. The characteristic blood vessel pathology of *B. pyocyaneus* infections was not found. There was no justification for the diagnosis in this case of *B. pyocyaneus* endocarditis on the evidence cited, although it is usually included in reviews of this subject.

CASE IX. This is a case of pneumococcic endocarditis cured by penicillin treatment. Tricuspid endocarditis due to *B. pyocyaneus* superimposed followed by death. (Fig. 6.)

H. S. was a forty-five-year-old, colored male who complained of pain and swelling of the right knee of three days' duration. For the week prior to admission he had been on a drinking bout. Three weeks prior to admission he had contracted a cold with a dry, non-productive cough, which had persisted for one week. No sore throat was noted.

The patient had had gonorrhea twenty-five years before. A similar episode of arthritis of the right knee of three days' duration had occurred two years prior to admission.

On admission his temperature was 102°F., pulse 140, respiration 26. The patient was acutely ill but in no great distress. Except for the above noted arthritis of the right knee, there were no significant abnormal findings. The heart was of normal size. There were no murmurs, thrills or abnormal pulsations. The lungs were clear and resonant.

Laboratory examination revealed the follow-

ing: White blood count 10,000 per c. mm. with a predominance of polymorphonuclear leukocytes. With the exception of a white blood count of 18,000 per c. mm. on the sixth day, the range was between 7,000 to 14,000 throughout. There was no anemia. X-ray of the chest revealed an area of pneumonitis consistent with pneumonia in the right lower lobe. Two days later this area was wedge-shaped and appeared to be a healing infarct.

Blood cultures from the tenth to the twenty-second day revealed from 4 to 381 colonies of pneumococcus type XII. From the twenty-third to the twenty-eighth day (death) the blood contained from 23 to 700 colonies of *B. pyocyaneus* per cc.

In the hospital there were daily chills, with septic type of temperature curve, ranging from normal to 106°F. For the first nineteen days in the hospital he was treated with sulfadiazine in doses from 6 to 12 Gm. per day. When the pneumococcus bacteremia was discovered he was also given antipneumococcus (rabbit) serum, without apparent therapeutic effect. On the twenty-first day, penicillin was begun; over a period of four days a total of 480,000 units was given. The pneumococci disappeared from the blood stream within approximately twenty-four hours after penicillin therapy was begun. However, from the twenty-third day until death the blood stream contained *B. pyocyaneus* daily. He continued the septic course, went rapidly downhill and died on the twenty-eighth hospital day.

*Pathology.* A small vegetation was present on the tricuspid valve. Culture revealed only *B. pyocyaneus* (35 per Gm. of vegetation). There was a thrombus in the pulmonary artery to the right lower lobe, and an organizing infarct of the right lower lobe. The only organism cultured from the valve, thrombus and infarct was *B. pyocyaneus*. This finding was confirmed by two different laboratories.

(To be concluded in the next issue.)

# Seminars on Rheumatic Fever

## Rheumatic Heart Disease in the Adult\*

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I WAS asked to describe rheumatic heart disease in the adult. This is very much like asking one to describe the entire subject of acquired heart disease, excluding arteriosclerotic and syphilitic heart disease. This task is altogether too big. I shall be content to make a few points that seem to be of reasonable importance.

*Etiology.* Much has been written and many opinions have been expressed regarding the cause of rheumatic disease. Some of these opinions have been dogmatic; others have been reasonable on the basis of knowledge. All of us have had the experience of observing a rheumatic attack following invasion of the upper respiratory tract by the hemolytic streptococcus. Some are convinced that this type of infection acts as a trigger mechanism for reactivation of the rheumatic process in the susceptible individual. Frankly, I do not think that this has been proven. On the basis of such a concept, some have claimed that if one could prevent invasion of the upper respiratory tract by the hemolytic streptococcus, further rheumatic damage to the heart might be prevented.

If one considers the data upon which the relationship of the hemolytic streptococcus to rheumatic disease has been postulated, the use of sulfonamides to prevent rheumatic recurrences seems to be rational enough. On the other hand, the study of other experienced workers suggests that there are many loopholes in the work thus far done in this direction. As for myself, I am not thoroughly convinced.

It may be that too little sulfonamide is

being given to these patients. On the other hand, it is well established that the patient may develop resistant strains to the sulfonamides. It is quite possible that we may be forced to abandon this entire form of sulfonamide therapy because of the by-effects it may have on the blood of the patient and, in a few cases, upon renal function. I do not know the real status of protecting patients against rheumatic recurrences with sulfonamide therapy. I have not entirely abandoned it in my practice but I do not rely too much upon it.

*Diagnosis.* Judgment as to when rheumatic activity has terminated poses an important problem. We have to decide when we can again mobilize the patient. It is very gratifying to find that the experience with large numbers of children here leads to the same general thought as my experience with adults over a long number of years. The help of laboratory tests cannot be depended upon in making a diagnosis of rheumatic activity. I believe that in the final analysis, the clinical manifestations of the disease are far more important in diagnosis (as well as in arriving at the difficult decision as to when active rheumatic disease has ceased) than is reliance upon any single test or combination of laboratory tests.

It was satisfying for me to find that this attitude toward clinical judgment is the one held here. Dr. Taran tells me that many patients whose sedimentation test, temperature, pulse rate, vital capacity and hemoglobin content have become normal may remain in the active stage of rheumatic dis-

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ease. He tells me that children often tell the story of rheumatic activity in their behavior. These children, when left to their own devices, tend spontaneously to curtail their physical activities; when possible, they retire to more sedentary ways of behavior. Unfortunately, this is not as common in my experience with the adult. The adult will force himself to go ahead. He resents a period of economic inactivity and resents that behavior which classifies him as being an invalid. I think, therefore, that judgment as to the termination of rheumatic activity in the adult is even more difficult than in the child.

*Rheumatic Activity.* We know that rheumatic activity in the adult manifests itself in several different ways. Some patients have a single attack with no recurrences throughout the remainder of their lives. More commonly, we find the polycyclic type in the adult as well as in the child. I am inclined to believe that if the patient were cared for adequately during each one of these attacks, he might well end his active rheumatic career with relatively minor cardiac damage. While he may have definite valvular scarring, he may be expected to carry on with little or no cardiac disability into late adult life. In some of these polycyclic types, more significant damage is done to the heart muscle than to the valves. Some of these cases continue to have mild rheumatic activity for years. This state is often most difficult to diagnose.

It is difficult for me to imagine that the structural changes which take place in the valves, as we see them in the adult, should be the result of an allergic reaction on the part of the patient. On the other hand, we have no good bacteriologic or immunologic way of detecting this mild, smoldering infection. Dr. Homer Swift considers throat cultures to be of great value in prognosticating reactivation of the rheumatic process. On the other hand, other observers do not

find this of such important diagnostic help. I am rather impressed with the fact that many rheumatic patients, either during the period of rheumatic activity or between rheumatic attacks, have negative throat cultures; and on the other hand, many rheumatic patients with positive hemolytic streptococcal cultures in their throats do not have or develop active rheumatic disease. A positive throat culture does not, therefore, necessarily signify rheumatic activity.

*Classification of Rheumatic Heart Disease in the Adult.* I would be inclined to classify rheumatic heart disease, as seen clinically in the adult, into four very general categories: (1) Active rheumatic fever with evidence of carditis, endocarditis, pericarditis—one or more of these combined. (2) Patients who do not show evidence of active rheumatic disease but who have healed valvular lesions. I am excluding myocardial lesions from this group, as we have no ready means of diagnosing these clearly. This group, therefore, includes cases who show physical signs of valvular disease plus a history of one or more rheumatic manifestations in childhood. (3) A combination of type 1 and type 2. In this type 3, we have probably, the commonest form of rheumatic heart disease. This is the form of active rheumatic infection with residual valvular scarring. It is the most difficult type to treat. These patients do not respond to the usual methods of treatment. Their cardiac manifestations are not relieved as effectively as usual by the commonly used types of cardiac therapy. I think it is safe to say that the patient who does not respond to the usual forms of therapy has active rheumatic carditis. It seems as if rheumatic infection interferes with the cardiac response to our available therapeutic procedures. We find that we can go only so far in controlling the cardiac symptoms with bedrest, digitalis and diuretics. (4) The same as type 3 but with an additional infection, i.e., bacterial

endocarditis. This occurs most commonly in the form of subacute bacterial endocarditis and is generally due to the viridans type of streptococcus.

This classification into four types does not bring out the fact that active rheumatic carditis is possibly as common in the adult as it is in the child. Those of us who deal with adult rheumatic heart disease are often impressed with the frequency with which cardiac symptoms are associated with "activity."

It is generally accepted that the most characteristic manifestation of rheumatic activity is the Aschoff body. It is fair to say that if autopsies on the rheumatic adult were done with sufficient care and serial sections of the heart were studied, we would be surprised to find that the great majority of adults with rheumatic heart disease who were considered to be clinically inactive, really show histologic signs of rheumatic activity. This observation is of the utmost importance in relation to the discussion of therapy aimed at relieving cardiac symptoms in the rheumatic patient. In the adult as well as in the child, the only manifestation of rheumatic disease which can definitely give us help in prognosis is rheumatic activity. I would call your attention to the fact that age does not prevent rheumatic activity. That has been well proven by postmortem examinations.

*Cardiac Manifestations.* I think we must bear in mind that the clinical signs of valvular damage as manifested during active rheumatic disease do not necessarily foretell the degree of valvular damage that may be present a year later. The scarring process is a gradual and progressive one. Experience has shown that it often is not safe to form a judgment early in rheumatic disease as to subsequent myocardial damage. I prefer to wait from six months to a year before estimating such damage.

Mitral stenosis as a manifestation of rheumatic disease has no prognostic value, except

in so far as it is probably better if this manifestation is postponed until early adult life than if it appears in childhood. I do not know why that is so. I think it would take a vast number of cases to determine the truth of this concept.

Auricular fibrillation of transient type appears frequently in the course of rheumatic disease. In my experience, this occurrence should be considered as one of the manifestations of rheumatic active carditis. One must bear in mind, however, that it may become a permanent arrhythmia and therefore, be present in a patient who no longer has active disease. It has been suggested that the prognosis is somewhat better in the presence of auricular fibrillation than when it is absent. I do not know of any carefully conducted studies which substantiate this view. There is certainly no question that when auricular fibrillation supervenes in a case of congestive heart failure; control of the cardiac rate is more readily effected than when auricular fibrillation is absent.

There is one point in the literature with which my experience disagrees. It has been said that rheumatic pericarditis is one of the most serious prognostic manifestations of heart disease. The chance of developing the disease in other structures of the heart is greater in pericarditis—so they tell us—than in any other single manifestation of rheumatic disease. In my own experience, particularly in adult rheumatic disease, I am impressed with the fact that rheumatic pericarditis, if that has been the chief manifestation, gives a rather good prognosis. Naturally, in such patients the myocardium may suffer. But again, this has not been my experience. Most of the patients I have observed, return to the pre-pericarditic level after an attack of acute rheumatic pericarditis.

I would particularly call your attention to the confusing picture of healed valvular lesion in an active rheumatic heart with

early or beginning bacterial endocarditis. The differential diagnosis is often extremely difficult. We may have embolic phenomena in both. We certainly have fever in both. Secondary anemia is also found in both instances. In other words, the clinical picture may be essentially the same. There are few clues to differentiate rheumatic activity from early subacute bacterial endocarditis. One patient, as a matter of fact, presented just such a picture. He had some fever which was low-grade and not bothersome. It was an enlarged liver that called his attention to the illness. He lost his desire to work. Careful examination at least twice daily did not disclose any other phenomena, and one was inclined to diagnose this case as reactivation of old rheumatic disease. His white blood count and sedimentation rate were normal. His murmurs had not changed. If it were not for three successive positive *Streptococcus viridans* cultures, we should have treated this patient as having active rheumatic carditis. After obtaining the positive cultures, penicillin therapy was instituted and within forty-eight hours the entire picture changed. The temperature dropped to normal, the patient began to gain weight and markedly improved within a short time.

I should like to call your attention to one more clinical manifestation of rheumatic disease not ordinarily emphasized in clinical diagnosis. I refer to recurring pulmonary infarction. I am speaking of the patient who runs a low-grade temperature and from time to time has signs in the chest but fails to respond to the usual therapy directed toward heart failure. This patient very likely has pulmonary manifestations which must be regarded as being part of the picture of active rheumatic disease.

*Treatment.* In the past few years, several experiments have been made on the use of massive doses of salicylates and on the administration of these drugs intravenously. On the latter point, I can see no advantage

in giving salicylates intravenously rather than orally since they are rapidly and well absorbed by the gastrointestinal tract. In our present state of knowledge, we should consider salicylate therapy only as a symptomatic measure, particularly effective during the painful manifestations of rheumatic polyarthritides, but not a specific means for the treatment and cure of rheumatic disease.

Convalescence in the adult suffering from rheumatic heart disease is approximately the same as it is in the child. We should wait until we are convinced by all the evidence available to us at present that rheumatic activity has ceased. Then we should wait a little while longer, perhaps a few weeks, before permitting the patient to resume physical activities. The patient may then progress just as rapidly as his condition permits. In most instances, when his active disease is treated properly he will recover very rapidly during the quiescent period. Unfortunately, our general hospitals do not have adequate facilities to take care of patients of this type. It is obvious that we need many institutions which are set up primarily for the care of the rheumatic patient who is not acutely ill and yet not quiescent, institutions whose aim it is to treat the patient until all evidence of rheumatic activity is terminated.

As to the time when the patient can be mobilized, it seems to me that it requires considerable clinical judgment to make this decision. Whatever the clinical signs may mean, my experience tells me that they are the most accurate of our tests for determining when the patient's rheumatic activity has ceased and when he can be mobilized. We hope that more objective criteria will be developed in the near future.

#### DISCUSSION

QUESTION: In the treatment of inactive rheumatic disease do you think that restric-

tion of activities would prevent rheumatic recurrences?

DR. EGGLESTON: I have never seen any evidence that it does. I think we in the medical profession like to err on the side of conservatism. But I do not think that physical activities, if kept within the limits of the patient's heart capacity, have any particular influence on the recurrence of rheumatic activity. What is your opinion in this matter, Dr. Taran?

DR. TARAN: Our experience with children and with young adults is precisely the same as yours. What the physician wants to know, I believe, is how to manage an adult rheumatic cardiac patient in order to prevent further cardiac damage and, above all, rheumatic recrudescences. Should the adult rheumatic cardiac patient be dismissed from the list of follow-up patients until such time as rheumatic activity occurs, or should he be kept under careful medical supervision during the rest of his life? In children and young adults, we are inclined to take a middle course. While we believe that these patients should be encouraged to resume normal activities as long as their rheumatic disease is quiescent, we do not like to lose sight of them for fear of overlooking an attack of mild rheumatic activity. What is your experience with the adult in this regard, Dr. Eggleston?

DR. EGGLESTON: I am also inclined to straddle the question. I allow patients to do anything within their myocardial capacity. I urge them into as hygienic a mode of life as possible. I encourage them to live as much as possible in the open air and sunshine, and in general, maintain as high a state of general physical health as possible. The advice is much like that given to a patient with arrested tuberculosis. In addition, I advise them to shun those in their environment who have frequent infections. But, I do not limit their life's activities unless it is evident that their cardiac reserve is low.

QUESTION: Do you believe that if a patient has quiescent rheumatic heart disease, full vigorous physical activity is likely to precipitate congestive heart failure at an earlier age, due to strain of the heart muscle?

DR. EGGLESTON: I think that in the absence of rheumatic activity, there is no evidence that physical work will precipitate cardiac failure. In other words, if the patient can perform any vigorous act without cardiac symptoms, he will sustain no harm from that act. I allow such patients to play games, indulge in sports, and even play vigorous tennis. I have seen no harm from it.

QUESTION: Is there any explanation why some patients will have only one attack and others have repeated attacks of rheumatic active disease?

DR. EGGLESTON: I have no idea. It is a fact that certain patients suffer one attack and go through life without any recurrences. I do not know why. In fact, I think it is safe to say that we do not know very much about the immunology of rheumatic fever. I do not even know that rheumatic fever is a bacterial infection although all evidence points in that direction more than in any other direction. Why one patient should get recurrences and another should not, is still a mystery.

QUESTION: Would you say then, that our habit of excluding children and young adults from competitive sports during the quiescent period of rheumatic disease is not based upon solid evidence?

DR. EGGLESTON: If the patient is symptom-free, I do not restrict him in any way. I think it is reasonable to say that once a patient has healed rheumatic disease, he can be classified in the same way as a patient who has had an incision into his body, an incision which has healed. I am inclined to say that such scars as may be left in the heart muscle which had not given any subjective or objective symptoms can be disre-

garded from the point of view of demands placed upon the heart muscle.

DR. TARAN: I think it is only fair to state, however, that the habit of keeping rheumatic children out of competitive sports is based upon the premise that since these children are not watched very carefully and frequently, one might overlook mild, smoldering, active rheumatic disease. It is during the period of active disease that we wish to protect the child from vigorous exercise. I am quite certain that if we could watch these children carefully, and be sure that there was no evidence of rheumatic activity, we would permit them any form of physical activity within the limits of their cardiac ability, irrespective of the presence of definite evidence of advanced valvular disease.

QUESTION: Is there any evidence that makes us believe that keeping patients in bed for a long period of time predisposes to pulmonary emboli?

DR. EGGLESTON: Yes, our habit used to be to keep such patients in bed for a long time. I do not now. I do not believe in rigid inactivity, even in a case of mild active rheumatic disease. Even in this instance, we do not get into difficulty if we do not impose excessive restrictions on these patients. Movement of the arms and legs is rather important.

QUESTION: Is there any special hazard in pregnancy and labor in rheumatic heart disease?

DR. EGGLESTON: I can dodge that question by saying I am not an obstetrician. We follow all our pregnancy cases very closely, together with the obstetrician. It is my experience that if during the course of pregnancy there is no evidence of a failing heart, it is safe to permit the patient to carry through and deliver normally. It is only when the heart shows definite evidence of failure that we interrupt the pregnancy. We do believe, however, that labor should be eased as much as possible. In my experience,

it is perfectly safe to permit the patient to go through the entire pregnancy while being controlled with digitalis. There is, of course, the other side of this problem—that is, a rheumatic cardiac patient who becomes pregnant is likely to lose the baby.

QUESTION: Would you favor digitalizing a patient with heart disease who becomes pregnant but who does not show signs of failure?

DR. EGGLESTON: I do not see any indication for that. We can nowadays digitalize a patient so rapidly, and with such a high degree of certainty and safety, that I do not see any reason for pre-digitalizing before evidence of heart failure appears. I think, however, that it is important to keep these patients under close enough observation to be able to pick up early or incipient decompensation.

QUESTION: Would you consider a slight increase in dyspnea in a pregnant patient with rheumatic heart disease as a sign of heart failure?

DR. EGGLESTON: First, we have to weigh all the clinical findings before stigmatizing a patient as having cardiac insufficiency. However, a degree of dyspnea greater than what would be normal for a patient who is pregnant should be considered as sufficient evidence of oncoming cardiac insufficiency. The apparent dyspnea that one sees in women after the fourth month of pregnancy, however, may not be cardiac.

QUESTION: Some years ago, at a meeting of the Heart Association, a paper was presented on the subject of pregnancy and rheumatic heart disease. The thesis at that time was that mitral stenosis gave a poorer prognosis in pregnancy and labor than minimal signs of heart failure. Do you subscribe to that, Dr. Eggleston?

DR. EGGLESTON: Frankly, I have not had sufficiently wide experience with that group of women to be able to form a sound judgment on that subject. It is my impression,



however, that from the point of view of pregnancy and labor the extent of valvular damage is less significant than insufficiency of the heart muscle.

QUESTION: Is active rheumatic disease an indication for terminating pregnancy in a case in which the heart is well compensated?

DR. EGGLESTON: I think active rheumatic carditis is a valid reason for terminating pregnancy from the point of view of both the mother and the fetus.

QUESTION: Is there any risk in interfering with the pregnancy in such a case?

DR. EGGLESTON: Very small.

QUESTION: Is the risk smaller than carrying the baby through for nine months?

DR. EGGLESTON: I think so. It is my impression that rheumatic patients who have fairly good hearts are good operative risks. I would go further and say that patients with heart disease are good operative risks except when there is definite evidence of heart failure or a high degree of active carditis.

QUESTION: Since we are on the obstetrical angle, I have come across a statement recently that when a rheumatic patient is found to have a rise in pulse rate above 110, and a respiration rate above 24 during the first stage of labor, digitalization is indicated. What is your experience in this direction?

DR. EGGLESTON: It is very reasonable to state that in a rheumatic cardiac patient, or in any cardiac patient, a rise in respiration rate during the first stage of labor should be

considered a sign of early decompensation. Digitalization therefore is indicated.

DR. TARAN: This discussion of rheumatic disease in the adult may be summarized as follows: It was pointed out that while the various manifestations of rheumatic disease may differ somewhat in the adult and in the child, the dominant consideration is the active rheumatic process and not the end result of cardiac damage. The important question in the management of rheumatic disease in the adult is when the activity has ceased and quiescence has begun. Treatment of rheumatic disease in the adult does not differ from that in the child since the important policy in treatment is good medical care during the acute process in both adult and child. A good deal of stress was placed upon clinical assessment of symptoms and signs as against reliance upon the laboratory methods commonly used for the diagnosis of acute rheumatic fever.

A workable classification for the types of rheumatic disease encountered in the adult was presented and some of the more unusual manifestations of rheumatic heart disease were described.

Some of the modern concepts of treatment were discussed but it was pointed out that continued bedrest during the active process still remains the most important means of discouraging further cardiac damage. Return to completely normal active life is advised in patients with rheumatic disease in whom it is reasonably certain that the active disease has terminated.

# Treatment of Acute Rheumatic Fever and Acute Rheumatic Heart Disease\*

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IT would seem presumptuous to attempt to discuss the treatment of rheumatic disease in one session. Such disproportion in the assignment of time might lead one to assume that this aspect of the subject is relatively unimportant. While it must be admitted at the outset that no specific remedies have been forthcoming, I believe we have learned a great deal about the treatment and management of acute rheumatic fever in the last few years. Experience with this "non-specific" treatment has already accumulated evidence to show that the outlook for the patient with rheumatic disease has definitely improved.

There are two schools of thought with regard to treatment of this disease. There are those who are definitely discouraged and have the attitude that rheumatic disease is a hopeless chronic illness for which little or nothing can be done. These workers in the field believe that all our energy and interest should be devoted to the study of the cause rather than the treatment of rheumatic disease. The second group of workers in this field believe that rheumatic disease should be treated somewhat like tuberculosis. We had gone a long way in the management of tuberculosis before the tubercle bacillus was discovered. Similarly, a good deal of progress in the treatment and management of rheumatic disease may be expected before the etiology is known.

## PREVENTION OF RHEUMATIC RECURRENCES

*Chemotherapy.* The factors which stimulated the vigorous attempts to prevent rheumatic disease are rather obvious. We know that rheumatic disease has a tendency to recur; and the more attacks, the more extensive the cardiac damage. The frequent combination of hemolytic streptococcal infections with rheumatic disease, and the ease with which streptococcal infections can now be prevented by chemotherapy all led, in recent years, to a flurry of attempts to prevent rheumatic recurrences. I believe it is fair to say that final judgment with regard to the efficacy of sulfanamides in preventing rheumatic recurrences must be deferred until further rigidly controlled studies are made.

*Climate.* Some years back, a great deal was said with regard to the effect of subtropical climate upon the natural history of rheumatic disease. Many patients have been sent to Florida, Arizona and Southern California in the hope of preventing rheumatic recurrences. The results to date do not give us enough solid evidence to show that residence in a subtropical climate definitely modifies the course of rheumatic disease. It must be said, however, that the appealing character of this form of therapy may definitely have its psychologic rewards, and may confuse final evaluation

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of the effect of climate, as such, upon the disease.

*Salicylates.* Many clinics, both in England and this country, have used salicylates in varying dosage as a prophylactic agent against rheumatic recurrences. Some clinics in England have administered salicylates to ambulatory patients over a large number of years. We have tried a similar experiment, using small doses of sodium salicylate during the winter months in patients who might be susceptible to rheumatic recurrences. To date, we have no evidence to prove that this form of therapy prevents rheumatic recurrences.

*Vaccination.* Many attempts have been made to vaccinate or inoculate patients with hemolytic streptococcal vaccines in order to prevent rheumatic recurrences. More work needs to be done in this direction to prove the relationship of such therapy to the prevention of rheumatic recurrences. It would seem to me that clearer insight into the immunologic responses of patients with rheumatic disease must be obtained before proper evaluation of this method of prophylaxis can be made.

*Vitamins.* The significance of vitamin B and, in recent years, vitamin C has not been fully explored in the matter of preventing rheumatic disease. The first encouraging evidence with regard to the rôle that vitamin C plays in rheumatic disease has been somewhat dimmed by lack of confirmation of reported results.

In summary, therefore, one is compelled to state that no method thus far proposed in the prevention of rheumatic recurrences can be relied upon to modify the natural course of rheumatic disease.

#### TREATMENT—ACUTE PHASE

*Salicylates.* Of all the therapeutic agents that have been used in the treatment of rheumatic disease, salicylates have stood the test of time. Many years ago, large

doses of salicylates were used with often startling therapeutic results. However, since untoward effects were observed frequently, and since it cannot be shown that salicylate therapy is a specific form of therapy, the use of massive doses was gradually discouraged.

The recent statement of Coburn that massive salicylate therapy may prevent the stigmata of heart disease reawakened interest in this form of therapy. However, evaluation of any therapeutic agent for rheumatic disease is fraught with so many difficulties and pitfalls that it is not easy to determine whether salicylates are beneficial or not. Suppression of the sedimentation rate does not always signify cessation of the active rheumatic process. Subsidence of all clinical and laboratory evidence of active rheumatic disease does not always mean that significant heart damage may not appear years later, without obvious recurrences of rheumatic disease. On the other hand, it has been observed that massive doses of salicylates often produce startling therapeutic results in making the patient symptom-free.

Our experience with salicylate in large or massive dosage may be summarized as follows: (1) Rheumatic polyarthritides responds promptly and effectively to large doses of salicylates. This result can be obtained by oral as well as intravenous use of salicylates. The intravenous route does not offer any advantage over the oral route. Massive doses of salicylates in this group of cases did not present any important toxic manifestations of salicylism. (2) Massive doses of salicylates used early in rheumatic carditis in children seem to produce equally prompt and effective results. Intravenous therapy in this group may be hazardous. (3) Small doses of salicylates do not seem to affect the course of rheumatic carditis. In this group, one finds that when salicylates are withheld or given in small doses evidence of active rheumatic disease continues for

weeks and months following cessation of therapy. (Fig. 1.) (4) Finally, massive doses of salicylates present definite hazards.

*Sanatorial Care.* The short period of observation and the small number of cases so far observed under sanatorium care preclude the formulation of statistically significant conclusions as to the lasting effects of sanatorium care. However, close observation of small groups of cases at the sanatorium, and of comparable groups of rheumatic children who did not receive sanatorium care, justifies certain deductions.

A large proportion of the children treated here at St. Francis are admitted from the cardiac clinic and the wards of the Kings County Hospital. The total number of Kings County children treated at the sanatorium during the first seven-year period was 373. During the same period of observation, 312 children were chosen from the clinic and wards of the same hospital as controls. Since inadvertent bias may play a significant rôle in the choice of cases for sanatorium care, painstaking efforts were made in choosing the control group, case for case. No convalescent care of any sort was offered to the control group of children.

The two groups of children were comparable as to age, age at onset of rheumatic history, number of rheumatic attacks, the extent of cardiac enlargement, and the incidence and type of rheumatic active infection observed at the beginning of the study period. (Table 1.) In addition, the two groups compared well as to the type of home environment before the study began and at the end of the period of observation. The results were as follows:

1. *Rheumatic Recurrences:* The number of rheumatic recurrences following sanatorium care is significantly smaller than in the control group. Both groups of children show a marked decline in recurrence rate as the time from onset of the rheumatic disease increases. The treated group, however,

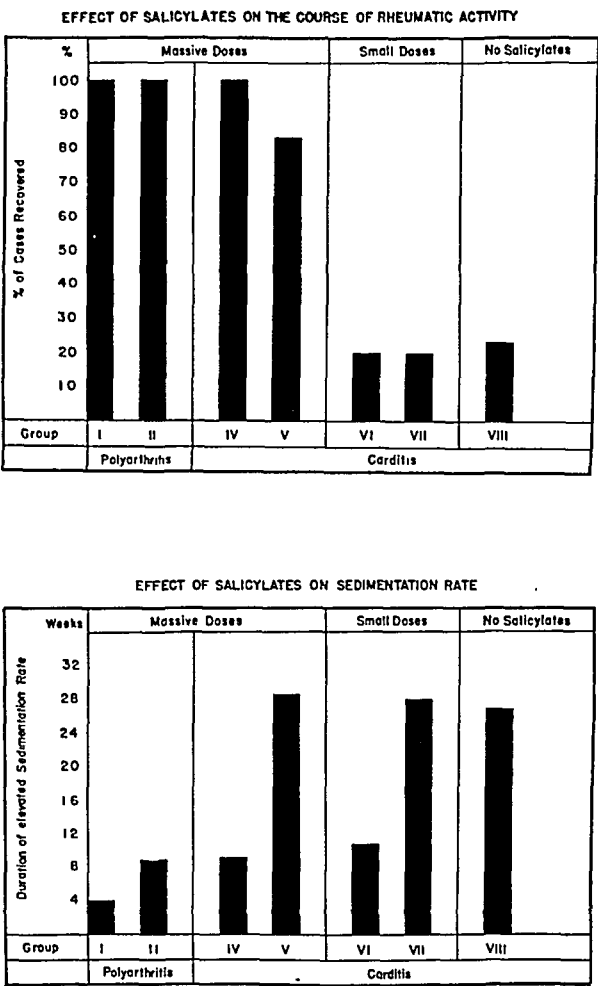


FIG. 1

FIG. 1. Group I: Children who received intravenous salicylates for rheumatic polyarthritis. Group II: Children who received massive oral doses of salicylates for rheumatic polyarthritis. Group IV: Children with rheumatic carditis who received massive doses of sodium salicylate by mouth at the onset of the rheumatic episode. Group V: Children with rheumatic carditis who received massive doses of sodium salicylate by mouth; treatment begun several weeks after onset of carditis. Group VI: Children with rheumatic carditis who received the usual small doses of sodium salicylate at the onset of rheumatic carditis. Group VII: Children with rheumatic carditis who received the usual small doses of sodium salicylate; treatment begun weeks after the onset of the rheumatic episode. Group VIII: Children with rheumatic carditis who did not receive any salicylates during the entire period of rheumatic activity. (From *J. Pediat.*, 27: 59-68, 1945. Courtesy of the C. V. Mosby Company, St. Louis.)

seems to escape a significant number of recurrences. The decrease in recurrence rate in this group is most marked at the beginning of the post-sanatorium period. (Fig. 2.)

2. *Cardiac Enlargement:* In our experience, the extent of cardiac hypertrophy in children seems to be a more accurate index of cardiac damage than the extent of valvular involvement. Children with large hearts

Coombs that before the question of life expectancy in rheumatic patients can be answered, at least thirty years must be allowed to elapse between the beginning and the end of observation in a large number of patients. Our numbers are small and the lapse of time even smaller. Nevertheless, the marked difference between the number of deaths in the sanatorium group as compared with the

Table I

Comparison of treated and control groups of children at the first observation		
Number of children studied	Control group 312	Treated group 373
At the beginning of period of observation		
Average age (yrs)	9.35	9.22
Average age at onset (yrs)	7.38	7.37
Duration of rheumatic history (yrs)	1.97	2.10
Number of attacks per child	1.67	1.82
Percent of children with unequivocal cardiac enlargement.	12.5	12.5
Percent of children having active rheumatic disease at the beginning of study.	18.7	19.8

have a much poorer prognosis than those whose hearts are only slightly enlarged. In this study, we considered a heart as enlarged only if the enlargement was unequivocal and diagnosed as such, both on clinical examination and by roentgen studies.

At the beginning of the period of observation about 12.5 per cent of both the treated and the control groups of children showed cardiac enlargement. The average age of our children at the beginning of the study was nine and a half years and the majority of them were seen about two years after the onset of rheumatic history. As these children grew older, the percentage incidence of cardiac enlargement increased in both groups; but the increase in the number of patients with large hearts was significantly greater in the control group than in the treated group. (Fig. 3.)

3. *Mortality:* It was pointed out by

control group of cases is worthy of comment. Of the total of 373 children treated at the sanatorium, eight died of rheumatic disease. Of the control group of 312 children, twenty-one were dead of rheumatic disease at the end of the same period of observation.

The mortality and life expectancy studies of Dr. May Wilson show that at the end of the first year from the onset of the disease, 2 per cent of the children died of rheumatic disease; by the fourth year, 5 per cent; by the seventh year, 10 per cent; and by the end of the eighth year, over 16 per cent. Our findings for the control group of children are analogous to those of Dr. Wilson. The treated group, however, shows a significantly lower mortality rate. (Fig. 4.)

In summary, it may be stated that seven years' experience with the sanatorium method of care for rheumatic children seems to show that this type of care favorably in-

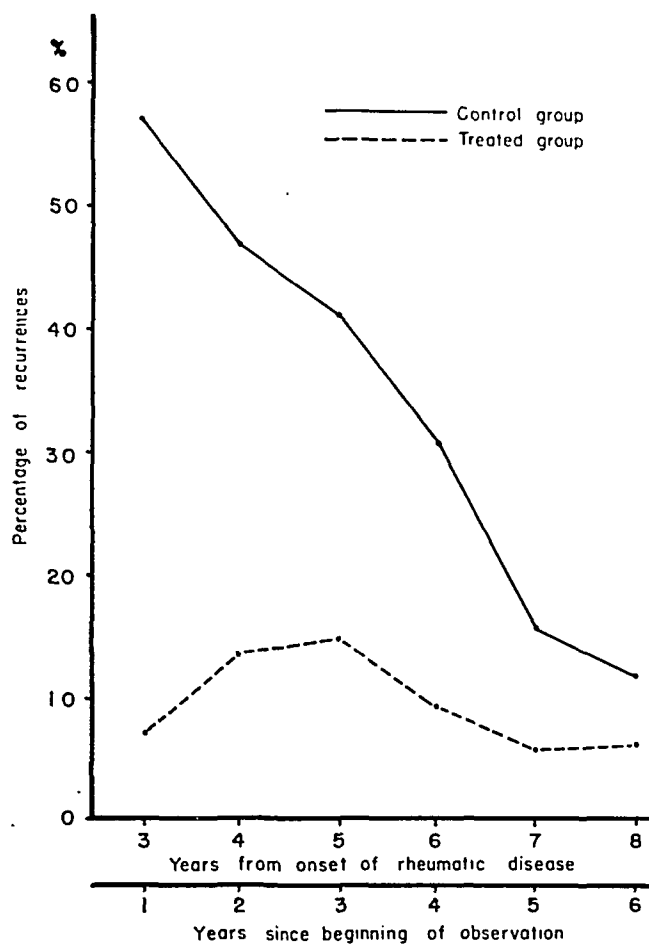


FIG. 2. Percentage incidence of rheumatic recurrences in relation to lapse of time since onset of rheumatic disease.

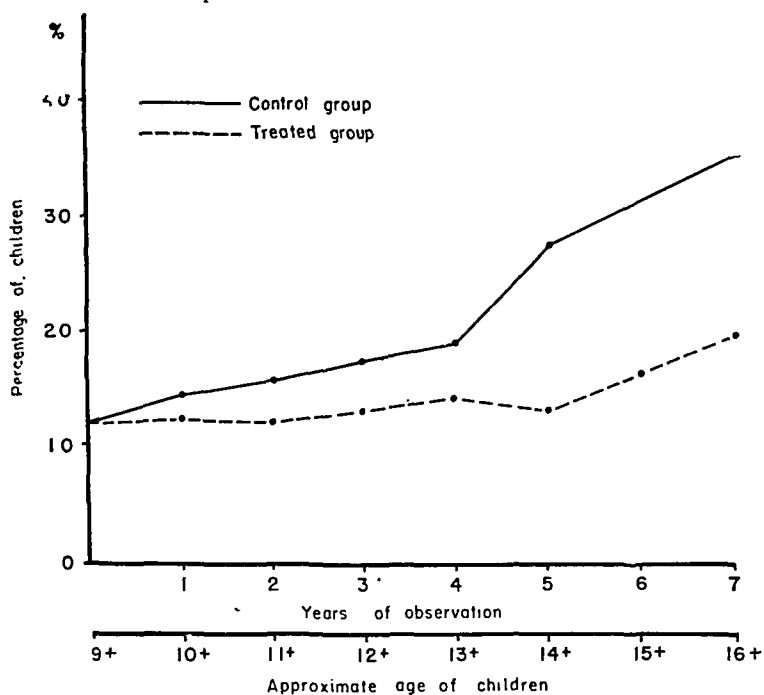


FIG. 3. Percentage incidence of children showing unequivocal cardiac enlargement.

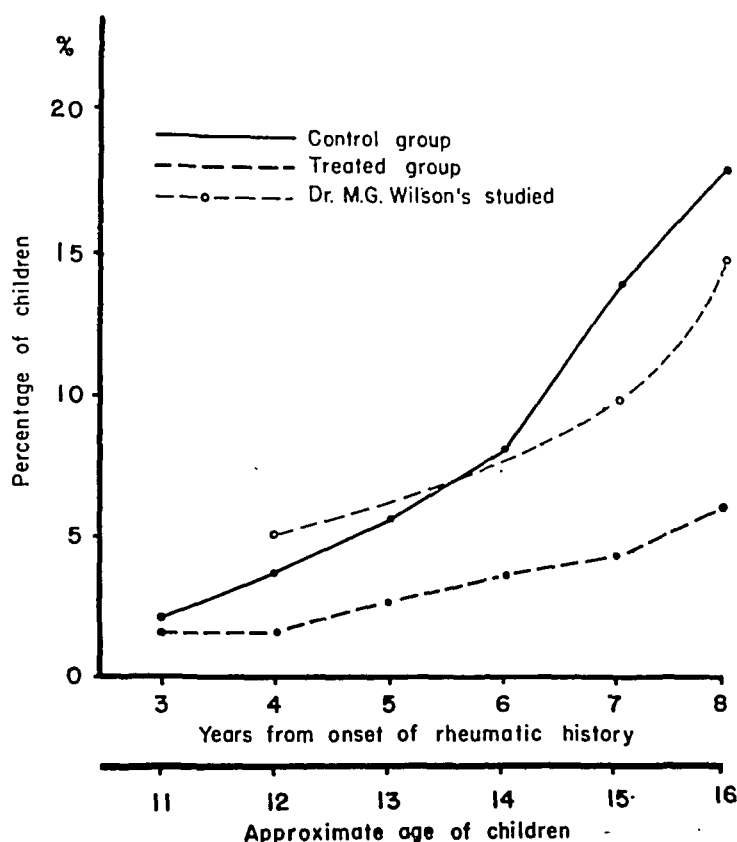


FIG. 4. Percentage incidence of deaths in rheumatic children in relation to lapse of time since onset of rheumatic disease.

fluences the course of rheumatic disease in children. It seems reasonable to assume that the significant decrease in the recurrence rate at the early stage of rheumatic disease when treated at the sanatorium may, in part, explain the low incidence of cardiac enlargement and the significantly lower mortality rate observed in the treated group of children.

#### TREATMENT OF RHEUMATIC HEART DISEASE WITH FAILURE

It is generally agreed that heart failure in rheumatic disease is almost always accompanied by rheumatic carditis. Thus, it is the belief of most clinicians that the pattern of failure in this form of heart disease differs in some respects from that observed in other forms of heart disease, in which the mechanical type of failure predominates. It is a reasonable assumption, therefore, that the usual form of therapy used in rheumatic

heart failure does not produce the beneficial effects usually observed in arteriosclerotic, hypertensive and other forms of heart failure. The use of digitalis, for instance, in rheumatic heart disease with failure rarely, in our experience, produces the desired effect. Mercurials and other diuretics do not produce the same startling diuresis in acute rheumatic carditis with failure as they do in other forms of heart failure.

*Digitalis.* Some observers believe that digitalis should not be used in acute rheumatic carditis with failure. Sir Thomas Lewis believed that "the use of digitalis for failure with congestion in rheumatic infection is not recommended." Derick, in 1936, stated that "the benefit of digitalis in active rheumatic carditis with decompensation is questionable." Tung, in 1936, made the observation that "although in general, auricular fibrillation with a rapid ventricular rate, is an indication for digitalis, the onset of this

rhythm in patients who have received large doses of digitalis, constitutes an indication that a toxic effect of digitalis is present. Further use of the drug might give rise to ventricular tachycardia or fibrillation or even irreversible cardiac damage." Schwartz and Levy during 1930 and 1931, found that "digitalis does not produce beneficial effects in rheumatic cases with decompensation even in afebrile cases."

Our studies on the use of digitalis in acute rheumatic carditis with failure agree, in the main, with these observations. We are impressed, however, with the fact that certain types or certain patterns of failure react somewhat more favorably to digitalis than others and that certain forms of acute carditis are much more sensitive to the toxic effects of digitalis than others. (Fig. 5.)

We have rarely observed any beneficial effects from digitalis therapy in acute rheumatic pancarditis with heart failure. Toxic effects of digitalis occur early, very frequently before the complete digitalization dose has been given. Several instances in which complete digitalization with the single dose method was attempted resulted in paroxysmal ventricular tachycardia and, in one instance, in ventricular fibrillation. Our experience would seem to warn strongly against the use of digitalis in this form of heart failure.

We have been unable in the vast majority of instances to relieve cardiac failure with digitalis when the presenting symptoms were those of left-sided failure. In such cases, depression of the ST interval and inversion of the T wave on the cardiogram, as well as premature ventricular contractions, occur early in the period during which digitalization is carried out. It would seem, therefore, that in this type of rheumatic heart failure digitalis is of little or no help.

In a few instances, when the presenting symptoms are both left- and right-sided failure, digitalis seems to relieve some of

DIGITALIS IN RHEUMATIC DISEASE WITH HEART FAILURE  
1930-1940

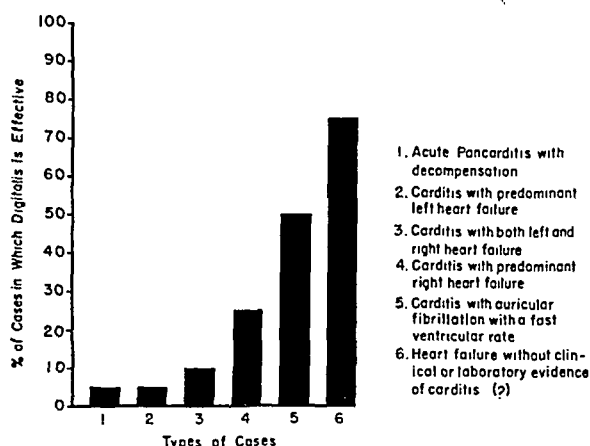


FIG. 5.

these symptoms. In this group of cases, therefore, it is worth trying.

In the rare instance in which the patient shows almost true right heart failure, digitalis seems frequently to produce the desired effect. Our observation, therefore, suggests that in this group digitalis should always be tried.

In our experience, only half of the cases with acute carditis with auricular fibrillation can be controlled with digitalis. In one of every two cases of auricular fibrillation suppression of the rapid ventricular rate could not be accomplished with complete digitalis therapy, and toxic effects of digitalis occurred before visible effective results could be obtained.

It is questionable whether one ever sees rheumatic heart failure without active rheumatic disease. Occasionally, one is impressed with the fact that all laboratory and clinical evidences of carditis are absent and the patient presents unequivocal signs of advancing failure. While it is admitted by pathologists that histological examination of these hearts would undoubtedly show evidence of rheumatic activity, the active process must be at a level which is below the clinical horizon. These cases react in the classical way to the use of digitalis.

*Mercurial Diuretics.* From time to time one sees in the literature a report on the use



of some of the xanthine group of diuretics in rheumatic heart disease. Our experience shows that there is no benefit to be gained from withholding mercurial diuretics; that these are the most effective diuretics; and that toxic effects from mercurials are extremely rare. We are impressed with the fact that the use of mercurials in rheumatic heart failure occupies a more important place than in failure from other causes. Not infrequently this form of therapy is a life saving measure. Advancing cardiac edema can be controlled effectively by means of mercurials until the active carditis is past and cardiac efficiency is increased.

*Oxygen Therapy.* The use of oxygen as a therapeutic agent in heart disease has been explored both in England and in this country for the past twenty-five years. Barach and his associates have studied the effect of oxygen therapy in various types of heart disease and concluded that in congestive heart failure and in acute coronary thrombosis oxygen is very often a life-saving measure. Poulton in England has demonstrated that patients suffering from rheumatic carditis with or without failure showed marked improvement when treated in a 50 per cent oxygen atmosphere. Our experience with oxygen therapy in rheumatic carditis in children in the main confirms the observations of Poulton. In cases with acute carditis of recent onset there is an immediate drop in temperature and pulse rate. The clinical behavior of the patient, the unequivocal improvement in cardiac reserve, and the dramatic removal of all subjective and objective signs of cardiac insufficiency, reflect the profound salutary effect of oxygen therapy upon cardiac physiology disturbed by acute rheumatic carditis. We are impressed with the fact that while rheumatic activity is not measurably shortened by oxygen therapy, the cardiac disability resulting from carditis is greatly minimized by decreasing the work of the heart during the acute inflammatory

phase. In addition, our experience shows that residence in a high oxygen atmosphere during the course of acute carditis removes the disabling and most annoying symptom of cardiac fatigue so commonly observed in children suffering from acute rheumatic carditis. This symptomatic relief enhances relaxation, sleep and nutrition, factors which undoubtedly contribute to rapid and satisfactory recovery.

#### CONCLUSIONS

It is clear from this brief discussion that much remains to be learned about the treatment of acute rheumatic fever and rheumatic heart disease. The prevention of rheumatic recurrences with chemotherapeutic agents is still in the experimental stage. The use of massive salicylate therapy in acute rheumatic disease remains an important form of therapy in acute rheumatic polyarthritis and at the onset of acute carditis. Digitalis, in our experience, is of limited therapeutic use in acute carditis with failure; mercurial diuretics, used judiciously during this phase of the disease, seem to be a satisfactory substitute for digitalis therapy. Long residence in a 45 to 50 per cent oxygen atmosphere during the course of acute carditis offers a definite means for reducing the work of the heart during the acute inflammatory phase and, in our experience, minimizes the cardiac damage resulting from acute carditis.

#### DISCUSSION

DR. TARAN: The subject of treatment of acute rheumatic fever and acute rheumatic heart disease with failure is now open for discussion. Are there any questions?

QUESTION: Your statement on prevention of rheumatic recurrences seems to indicate that none of the proposed methods of prevention has proven to be efficacious. And yet, it has been the experience of many practicing physicians in recent years that the judicious

prophylactic use of chemotherapy seems to stop the progress of rheumatic recrudescences. Some of us have been impressed with the distinct improvement in the rheumatic status of the patient when he is transferred to a warm, dry climate. Occasionally one sees unmistakable progress in the natural history of rheumatic disease by careful attention to nutrition and vitamin intake of the rheumatic patient. Furthermore, we are told that rheumatic children in a good physical environment weather the storm of rheumatic disease better than those in a poor home environment. These more fortunate children have less recurrences and, by and large, sustain less cardiac damage. There should be some explanation for this testimony culled from everyday practice.

DR. TARAN: You are quite right that much testimony can be gathered in private practice to show that rheumatic disease can be treated effectively. I am, however, not certain that any such evidence exists to show definitely that rheumatic recurrences can be prevented by the methods you mention. A wide experience with these patients over long periods of time seems to indicate that good medical and nursing treatment of the acute phase of the disease is, for the present, the best insurance against so-called recurrences. We are impressed with the fact that in most instances recurrent attacks are reactivations of a subacute active process rather than truly *recurrent* attacks. Once the active process has come to an end, a recurrence is unlikely. This may explain the often striking difference in the end results in patients who receive careful medical attention and those who are neglected during the course of mild rheumatic activity. The incidence of rheumatic recrudescence after good sanatorium care is indeed small and matches favorably the good results obtained by a change of climate, chemotherapy and a high vitamin intake. In sanatorium care the principal aim is prolonged treatment of the

acute phase until all clinical evidence of active disease has subsided. Change of climate or the institution of a special regimen of chemotherapy or nutrition may often be associated with a careful regard for other factors—more rest, less exposure to chilling, etc., all of which may have a salutary effect upon the mild, smoldering rheumatic process.

Much remains to be learned about rheumatic recurrence as distinct from reactivation. For the present, we are impressed with the fact that the therapeutic measures which seem to affect favorably the course of the active process of the disease insure, at the same time, the most effective way of preventing recurrences. Rheumatic activity, even of the mildest type, with manifestations that are subclinical, often needs only an apparently insignificant provocative stimulus to be transformed into a severe, stormy reactivation or “recurrence.” Complete quiescence in children, in our experience, only rarely is followed by recurrent attacks.

QUESTION: We are told that sodium bicarbonate when given in conjunction with sodium salicylate depresses the salicylate level in the blood. Does bicarbonate, therefore, interfere with the therapeutic effectiveness of salicylates?

DR. TARAN: We have not found it difficult to reach an optimum salicylate level (350–400 micrograms) in the blood serum when bicarbonate was used. Our custom is, however, to use small doses of bicarbonate, not more than half the salicylate dose. Our success with salicylate therapy was obtained only when an optimum serum level was reached.

QUESTION: How do you recognize salicylate intoxication? What is the mechanism of the intoxication?

DR. TARAN: The clinical picture of salicylate poisoning has been known for many years. It is characterized by extreme dyspnea; irritability and restlessness; nausea and

vomiting; dehydration and eventually disorientation, paralysis, coma and death.

The mechanism of this intoxication is not known. Several theories have been advanced: (1) Acidosis leading to hyperpnea has been considered as the main underlying cause; there is little evidence for this thesis. (2) Direct stimulation of hypothalamic nuclei causes hyperpnea which leads to acidosis; the acidosis due to hyperventilation may cause an increased metabolic rate, and this in turn, depletes the glycogen reserve; some have shown a direct loss of glycogen in the liver, thus interfering with the hepatic enzymes. (3) Increased metabolic rate; not substantiated. (4) Prolongation of the prothrombin time is an important factor. Toxic injury to the small blood vessels is the primary lesion—increased permeability of vessels.

The pathological findings are: (1) generalized petechial hemorrhages, varying in size from pin-point to large hematomas, have been observed in the brain, lungs, myocardium and mucosa of the stomach; (2) general congestion of the organs.

We have not observed severe bleeding resulting from massive salicylate therapy. In our experience, the hypoprothrombinemia which occurs in massive salicylate therapy can definitely be prevented or reversed by the use of vitamin K in small doses.

Intoxication from sodium salicylate is rare, and should, for the present, be regarded in the category of idiosyncrasies. Since, however, it is used so extensively in rheumatic disease, these idiosyncrasies should be watched for with concern. While the hazard is real, we have observed definite and severe salicylate intoxication in only three cases in a period of ten years. This low incidence of severe intoxication may be due to early recognition of poor risks for salicylate therapy. About 3 per cent of the patients treated with massive doses are poor risks for this form of therapy.

QUESTION: What distinguishes sanatorium type of care from good home or hospital care? It is not possible to carry out a sanatorium type of care in the home of the patient or on the wards of a well equipped pediatric service?

DR. TARAN: Yes. There is certainly no magic in the word sanatorium. The sanatorium is established on the principle that rheumatic disease in children in the acute stage cannot be adequately treated under conditions present in the usual children's hospital. It is a disease of months' or years' duration and the active period, no doubt, lasts much longer than the clinical manifestations, as we understand them now, would seem to show. Careful and detailed observation of elusive manifestations of the subclinical phase of the disease are of importance in the matter of preventing reactivation and progressive cardiac damage. This patient attention given over a period of many months cannot be carried out in the impatient environment of a hospital for acute diseases.

Furthermore, the sanatorium is set up to deal with the many psychologic, educational and sociologic problems inherent in protracted illness. To carry out such a program, the personnel of the sanatorium must be trained for this specific task. Such trained personnel is not to be had, at present, in most hospitals established for the treatment of acute disease.

With good intentions and a full understanding of this disease by the physician, nurse and parents, sanatorium care can indeed be carried out satisfactorily in the home of the patient. But since rheumatic disease is a poor man's disease, private care at home is completely prohibitive financially for most of the patients.

QUESTION: It would seem from your statement that digitalis therapy in rheumatic heart disease with failure in children is of limited value. Is this true also in adults?

DR. TARAN: Some observers believe that cardiac decompensation in a rheumatic heart is always indicative of active rheumatic disease, irrespective of the age of the patient. In our experience with young adults, this seems to be true. In these, digitalis therapy is of limited value. It is well known, however, that so-called "pure" mechanical failure is much more frequently encountered in the adult rheumatic cardiac than in the child. In these, digitalis produces the usual favorable effects. Auricular fibrillation is more common in the adult than in the child. In this group digitalization is the therapy of choice. On the other hand, one is frequently impressed with the number of digitalis failures in adult rheumatic cardiacs particularly when the symptoms of decompensation are predominantly those of left-heart failure. When the signs of active carditis are clear, digitalis therapy is often disappointing in the adult as well as the child.

QUESTION: Is there any physiologic explanation for the apparent beneficial effects of oxygen in acute carditis?

DR. TARAN: Much remains to be learned about the mechanism of oxygen therapy in heart disease in general and in rheumatic carditis in particular. A full answer to your question cannot, therefore, be given.

I am impressed with the concept, however, that overactivity of the acutely inflamed heart muscle fiber must be physiologically unsound and may be responsible for disturbance of the chemical and mechanical integrity of the heart muscle. An accelerated cardiac rate may further deplete cardiac efficiency by diminishing diastolic coronary filling, accentuating an already existing anoxemia of the heart muscle. Anoxemia of the heart muscle results in further disturbance in cell metabolism of the muscle fiber.

It is reasonable to assume that a form of

therapy which diminishes cardiac overactivity during the course of the acute inflammatory process might prevent the damaging end result of acute carditis. A significant decrease in cardiac rate alone diminishes the work of the heart, the working capacity of which is already impaired by local tissue anoxia. Decrease in cardiac rate might further improve the local tissue oxygen want by improving coronary filling. If this form of therapy would in addition raise the oxygen saturation of the arterial blood, which is critically diminished in cardiac patients, cardiac disability could be significantly prevented.

In our experience oxygen therapy in rheumatic carditis meets all these requirements.

#### SUMMARY

The treatment of acute rheumatic fever and acute rheumatic heart disease with failure was discussed in this morning's seminar. The efficacy of chemotherapy in the prevention of rheumatic recurrences was questioned. Massive salicylate therapy for acute rheumatic fever was considered effective in changing the course of rheumatic polyarthritis and early carditis. The benefits derived from sanatorium type of care for the protracted case of rheumatic disease were described and the principles underlying the aims of this type of care were delineated. Digitalis in the treatment of acute rheumatic carditis with failure was considered of limited value. Finally, the use of high concentrations of oxygen in the treatment of acute carditis was discussed. It was pointed out that while oxygen therapy may not influence the duration of rheumatic activity, it seems to lessen the cardiac disability resulting from carditis. Some of the physiologic principles responsible for the salutary effects of oxygen therapy were presented.

# Conference on Therapy

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## The Dose of a Drug

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. McKEEN CATTELL: In opening the therapy conferences for the current academic year, I would like to call your attention to the fact that this represents the tenth year in which these conferences have been conducted. As you know, they are recorded; selected ones are published in the *New York State Journal of Medicine* and now also in the new journal, *The American Journal of Medicine*. Formerly it was possible for us to supply reprints, and these have been quite popular amongst the students and staff of the institution. I regret now, however, that through an arrangement with The Macmillan Company, who are publishing an annual volume of *Cornell Conferences on Therapy*, we have agreed to discontinue the distribution of reprints. I hope the journals are available to most of you.

I would like again to bring up a point which we do every year, namely, our wish and our hope that the students will participate fully in the discussions. As you know, the purpose of these conferences is to provide a medium for informal exchange of views between the various groups who are interested in the problems, and we are eager to have the students take part in the questions and comments. Often in the warmth of the discussion, there has been too much of a tendency to confine it among those in the front rows, but it will be our constant endeavor to have all of you participate.

The subject of the conference today is "The Dose of a Drug." We think this is an important topic. There are many points of information concerning it which are provided by experimental pharmacology, and these have not always been fully utilized in drug therapy. The discussion will be opened by Dr. Gold.

DR. HARRY GOLD: I am going to deal with a few matters which bear chiefly on problems of dosage. I believe that dosage is one of the very weak spots in drug therapy. A large proportion of the failures in drug therapy results not so much from the choice of the wrong drug, but from the use of the correct drug incorrectly. The fault lies in the dosage. The single dose is either too small or too large, or the dosage plan is, for one reason or another, unsuited for eliciting the full power of the drug for the particular situation. Examples will help to clear the points I wish to make. And right here I should like to state that any resemblance of this to a discussion on cardiology is purely accidental; I shall simply draw on some of the cardiac drugs for purposes of illustration. Whenever I see a patient in heart failure who I judge ought not to be in that state, and who proves the fact by quickly recovering when placed on an appropriate system of treatment, I almost invariably find that the patient has already received the drugs which are generally used for the treatment of heart failure; a salt-free diet

has been prescribed; digitalis has been given; and one or another diuretic has been in use. The failure to achieve satisfactory results was due to improper dosage; the salt intake was not sufficiently restricted; the amount of digitalis may not have been enough; and the system of administration of the diuretics was inadequate for the needs.

A few years ago, we published some studies advocating the use of an "average full dose" of digitoxin to be given at one time for digitalizing patients in heart failure. We encountered many obstacles to the acceptance of this idea. It was argued that the susceptibility of individuals differs, that a single average dose will not be enough for the tolerant patients, and will poison the more susceptible ones. You may have seen the paper which appeared August 1945, in the New York State Journal of Medicine, in which the author stated: "It is absurd to speak of digitalizing a patient on 1.25 mg. of digitoxin." He then added: "There never will be a single dose of digitoxin or any other glycoside which will uniformly digitalize all patients regardless of the age, the sex, the weight, or the general condition." The fact that such a statement was made indicates that some persons apparently believe that such a dose exists, namely, a dose which will digitalize all patients uniformly. Our attention was fixed on this statement by reason of the fact that this heresy was, by implication, ascribed to us. I have heard others voice disappointment with our proposed plan for the use of an "average full digitalizing dose" of digitoxin at one time, because in limited experiences it had failed to produce an expected degree of therapeutic results. It soon became clear to us that what troubles most people is the meaning of the term "average dose." We had a conference on digitoxin last year in which considerable time was spent in the endeavor to crystallize the meaning of the term "average dose."

The term "average dose" is very loosely used in therapeutics. We discovered, in that discussion, that the term is sometimes applied to the dose which produces the full effect in practically all cases. More often, it is applied to the dose which the "average physician" uses without regard for the origin of that usage. It is hardly necessary to point out that the "average dose" and the dose which the "average physician" prescribes are not the same.

In pharmacology, the term "average dose" has a fixed meaning. It is the dose which exerts a particular effect in 50 per cent of a population. When the end point is a lethal effect, it is referred to as the "average lethal dose" or the LD50.

The "average dose" in the pharmacological sense may also be determined in humans, and by substantially similar methods. Again, let us use an example to illustrate the method. If we were to start out to determine the "average dose" of digitalis which produces a T-wave change in the electrocardiogram, this is how we might proceed: We might start with 100 persons, we might give to each 0.1 Gm. digitalis, and twenty-four hours later we might take an electrocardiogram in order to see what percentage of the subjects showed a change. A month later, after the effects of this dose have disappeared, we might give the same group 0.2 Gm. digitalis, and again see what percentage showed an effect in the electrocardiogram twenty-four hours later. This procedure might be repeated at monthly intervals with increasing doses. At the end, we would have certain data, namely, a series of increasing doses and a corresponding series of increasing percentages of responses. If we then plot one against the other, we obtain a curve as illustrated in this diagram. (Fig. 1.) It is called a frequency distribution curve. This curve provides us with two kinds of information. It shows what the "average dose" is to produce the particular effect, namely, that

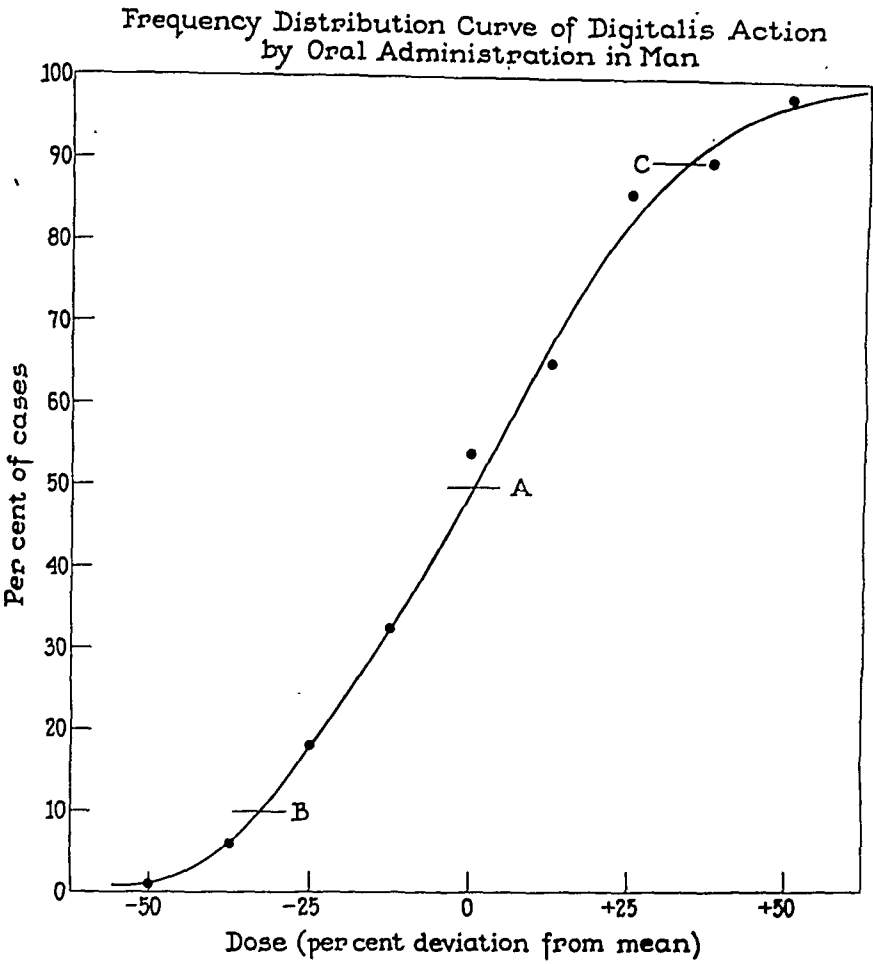


FIG. 1.

dose which produces the effect in one-half of the population. The shape, the steepness, and the length of the curve also show us the range of variability in the sensitiveness of the human population with respect to the particular drug and particular effect.

Such a curve gives us additional information. It tells us how useful an "average dose" for a given drug is likely to be. If the curve happens to be a fairly short and steep one, it shows that the sensitivity of one person differs very little from that of another, and that if, in such a case, the "average dose" were to be given to all, the results would be very satisfactory since some would show the precise therapeutic response, and the remainder, only a little less or a little more than the exact therapeutic end-point. On the other hand, if the curve is fairly long and flat, it shows that the sensitivity of one per-

son differs greatly from that of another; the scatter may be very wide; and the limits so extreme that one patient may require ten or twenty times as much as another to produce the same effect.

If a drug were to show such a long and flat frequency distribution curve, the "average dose" for this drug would not be very useful. One would have to start therapy with much less than the average dose in order to avoid poisoning the more susceptible members of the population.

We have determined the curve for digitalis. It is fairly steep and short. If 100 persons were to receive the "average dose," as you see on the diagram, about 75 of them would show the following results: Some, would show exactly the desired response; some, responses from doses down 25 per cent less; and some, responses from doses up

to 25 per cent more. Almost all are included in the "average dose"  $\pm 50$  per cent. Since we know that the end-point in digitalization is not very precise, such variations would, for the most part, escape detection, and even the occasional extremes would not cause serious poisoning. In the case of digitoxin, therefore, the "average full digitalizing dose" is a most useful unit of dosage.

Well, we know how these matters stand in the case of digitoxin, but for the vast majority of drugs in common use we do not have a frequency distribution curve in humans, and we do not know what the "average dose" is. Consider the case of epinephrine for the treatment of an attack of bronchial asthma. Where on the curve (see Fig. 1) does the usual dose stand? If the usual dose which is employed should happen to stand down at the point B, it would mean that it is too small, and that with the usual dose, there may be an unnecessarily large number of failures to produce the effect we are after. On the contrary, if the dose which we commonly employ should happen to stand at point C on the curve, it might indicate a dosage level in which we are obtaining an unnecessarily large number of cases of poisoning or undesirable side-effects. The fact remains that we do not know the "average dose" of epinephrine. Nor do we know the "average dose" of physostigmine for the treatment of abdominal distention, the "average dose" of morphine for pain, the "average dose" of phenobarbital for sedation, or of castor oil or magnesium sulfate for cathartic action. Here is a perfectly simple pharmacological conception which is readily accessible to application in patients, but in the clinic we continue to trundle along in the matter of dosage on more or less accidental and empirical experiences. So much for the "average dose."

The next point I should like to discuss is the dosage plan. There are essentially two types of dosage plans; one, the cumulative

dosage plan; and the other, the non-cumulative dosage plan. By the cumulative plan, we mean a plan of dosage which involves giving a small dose at the beginning and repeating at such intervals as to build up a concentration in the blood or the tissues adequate to produce the therapeutic effects. This method is used in the interest of safety. If the single full dose is unknown or is dangerous, as it is in most cases, the full dose is built up by steps, each of which in itself causes no harm or no serious toxicity. The ideal system involves knowing when the peak effect of any dose is reached. If the peak is reached in two hours after an oral dose, let us say, the interval between doses should be two hours; if the peak effect is reached in six hours, then the interval between the fractions should be six hours. The use of quinidine is a good example. If the objective is to bring to an end an attack of auricular fibrillation or ventricular tachycardia, one should start with a small dose, say 5 or 10 gr., and since it is known that the peak effect is reached in about two to three hours, repeat the dose at such intervals until enough has accumulated to produce the desired effect. The total amount of the drug does not matter. There can be no talk of failures unless such a cumulative system has been put into operation with the end-points being the therapeutic results or minor toxic symptoms. PicROTOXIN in the treatment of barbiturate poisoning is another good example. In such a case we often do not know the true depth of the narcosis or the dose of the barbiturate. We start with a small intravenous dose which could not do anybody any harm. To the peak effect of this, which is reached in about ten or fifteen minutes we add the next dose, and so we continue by steps until a concentration is reached which begins to produce therapeutic results. So much for the cumulative system.

The non-cumulative plan is just the reverse. It involves giving a single effective



# Conference on Therapy

## Dosage Systems

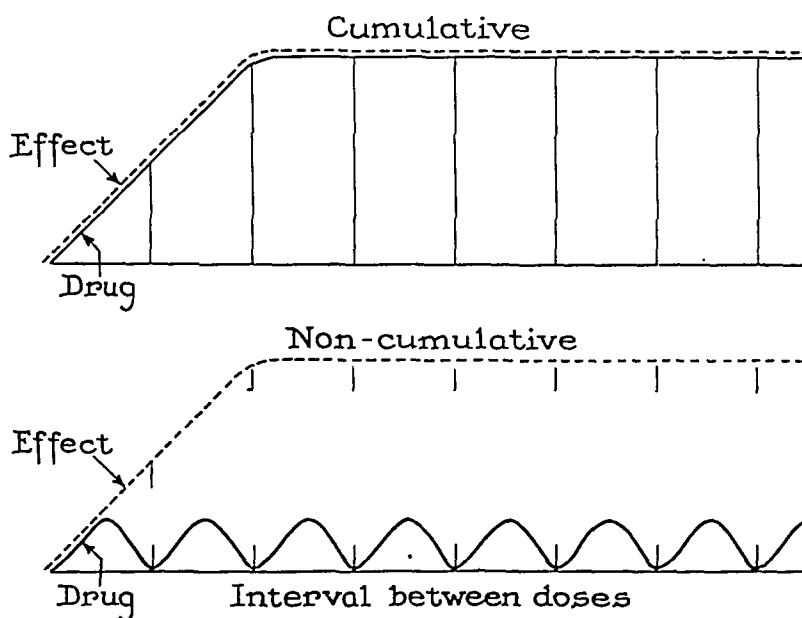


FIG. 2.

dose, but repeating it at such intervals as will prevent raising the concentration in the blood or the body tissues. Here the results may be cumulative, but the drug is not. The use of the mercurial diuretics is a good example. If the loss of weight of the patient with edema is the measure of the therapeutic effect, the plan is to repeat the dose at such intervals as to produce progressive loss of weight, but without significant increase in the concentration of the mercurial in the body above that of the first dose. Since these drugs are excreted in about twenty-four hours, the repetition of the dose at daily intervals provides a suitable non-cumulative plan.

These diagrams (Fig. 2) illustrate the two systems of dosage which apply to the majority of drugs. One is the system of rising steps, each in itself without danger; and the other is a system of complete curves of absorption and elimination. As I have indicated, in order to put these mechanisms into most effective operation, we have to have several bits of information. We should know about how quickly the drug is absorbed, the time it takes to reach a peak effect, and some-

thing about the speed of its elimination or duration of action. In this connection, there is the fact that cumulation is a self-limiting process for the majority of drugs. If one gives a patient a dose of 1 Gm. of sodium bromide every day, one finds that the blood concentration of bromide begins to rise, and continues to do so for two or three weeks. The blood concentration curve then levels off even though the same daily dose is continued indefinitely; an equilibrium is reached between the daily dose and daily excretion. In the case of digitalis, we see the same phenomenon at work, although we detect it in a different way. If a patient with auricular fibrillation and an apex rate of 140, receives 0.2 Gm. of digitalis every day, the apex rate begins to slow; it gradually declines to a level of about seventy a minute below which it may not go even though the same daily dose is continued indefinitely. First there was the period of cumulation, then the period when cumulation no longer occurred.

The duration of the period of cumulation differs for different drugs. In the case of digitalis, a fixed daily dose may show cumulation for two to three weeks before the

effect levels off. One cannot be sure that the patient will not become toxic, when using a fixed daily dose, unless it has been used for about three weeks in the case of digitalis. On the contrary, in the case of quinidine, cumulation ceases in about three or four days; if a patient receives, let us say, 1 Gm. of quinidine every day, the second day may show greater effects than the first, and the third may show greater effects than the second, but after the fourth day the effects are likely to level off and no further cumulation is apt to occur after that. These periods are not fixed with precision, but it is of the order of four or five days for quinidine and of the order of two to three weeks for digitalis.

There is still another point, namely, that the level at which cumulation ceases depends on the size of the daily dose. By way of illustration, cumulation of digitalis with a daily dose of 0.1 Gm. may level off at an apex rate of 100 a minute, while with a daily dose of 0.2 Gm., at an apex rate of 80. So also, in the case of the bromides cumulation ceases at a lower blood concentration of bromide when the daily dose is 1 Gm. than when it is 2 Gm.

There is no doubt that the points which I have discussed as requiring attention in rational systems of dosage play a part in the use of drugs as practiced at the present time. I have little doubt that the doses which are prescribed in the case of some drugs are actually the "average doses." Cumulative and non-cumulative systems are at work in dosage plans that are commonly used, but I am inclined to think that their operation is more by accident than design. For that reason, we find cumulative systems employed in cases where non-cumulative systems would give immeasurably better results and vice versa.

To find illustrations, one does not have to go very far. It is one of the most common of experiences to encounter patients receiving, let us say, 0.3 Gm. of quinidine three times a

day for weeks on end for a particular disorder of rhythm without producing any beneficial effects; one could have predicted the failure at the end of the fourth or fifth day. Since the system did not provide enough cumulation in the first four or five days, there remained nothing to do but to raise the single doses or to give fractions at shorter intervals during the day. You will find several reports in the literature, for example, pointing to the percentage of cases with auricular fibrillation in which quinidine succeeded in establishing a normal rhythm. What meaning have these percentages? If you will examine these reports you will find that a rigid dosage was used for all. That is no way to find out how effective quinidine can be.

Morphine is often given by hypodermic injection in urgent situations at intervals of ten or fifteen minutes. There can be no meaning in such intervals, since so little of the first dose is absorbed, the peak effect of the first dose being reached in from thirty to forty-five minutes, or in some cases longer. I have seen prostigmine used for abdominal distention in doses at intervals of six or more hours. The first dose produced no effects, and neither did the others. The effects wear off within about two hours. Here, then, is a system of dosage which could by no possibility elicit the therapeutic effects of this drug. And when I hear it said that a particular drug was without value in the case in question, I ask at once, how do you know? Was it used in such a manner as to make sure that there was here a case which could not respond favorably? The mercurial diuretics are recommended in the textbooks to be given at 4-day intervals. The mercurial is excreted within about twenty-four hours. To spread the interval to four days, simply allows a long period to elapse in which the patient receives no treatment, and in this time the condition remains stationary or deteriorates. It serves no pur-

pose other than to prolong the period of recovery from the heart failure.

Mapharsen in the treatment of syphilis is another case which requires attention from the standpoint of the present discussion. A dose is almost completely excreted in two to three days, and while there are some advocates of rapid methods which appear to take this into account, the most popular dosage plans call for only one injection a week.

The cumulative and non-cumulative systems of dosage do not exhaust the problems of dosage. There are situations in which a more or less fixed plan of dosage needs to be used without adjustments for the needs of the particular individual. These are cases in which precise therapeutic end-points or minor toxic end-points are not available as a guide to the adjustment in dosage. A good example is the use of digitalis in the heart failure of rheumatic active carditis. Here the therapeutic results are often indecisive and if one attempts to increase the concentration by the cumulative method, one frequently encounters troublesome and sometimes dangerous toxic symptoms. It is, therefore, best in such a case to adopt a fixed system of dosage with the highest prospects of therapeutic benefits and lowest liability of producing toxic effects, and to use that system in all without attempting to increase the dose to meet the needs of the particular case.

Therapeutic effects and minor toxic symptoms are the chief guides to adjustment of dosage in the cumulative systems. There are, however, cases in which special devices are used for that purpose. For example, in the case of insulin in diabetes, the adjustment of dosage depends to a large degree on the amount of sugar which appears in the urine rather than on any specific effects on the patient, although the latter factor is taken into account. Another specific method for adjustment of dosage is shown by the case of Hemophilus influenzae rabbit serum. Here

the dosage may be determined by the immune properties developed in the patient's serum or the immunity reaction after an intracutaneous injection of the specific antigen.

I do not believe that we have the time to go into the details of these special problems in this conference.

DR. McKEEN CATTELL: I would like to make one remark in relation to your curve, Dr. Gold, which I think may help to clarify the principle which determines the maximum extent of cumulation over a period of time. A cumulation curve, such as you drew, with a maximum or ceiling effect, represents the cumulation of the effects from the single doses, and is determined by adding the separate curves for each point of time. Thus, one has a whole series of curves of drug effect and the actual cumulation is measured by the sum of the effect of each of the doses at any point on the time axis. Once the point is reached at which the effect from the first dose disappears, then the added effect will be equal to that which is dissipated, and the curve will level off. So the explanation of cumulation from repeated doses is not obscure, but involves the knowledge of a very simple pharmacologic principle in relation to the persistence of the effect of a drug.

DR. CARY EGGLESTON: There were two items in Dr. Gold's discussion that I thought deserve comment. Dr. Gold discussed the term "average dose." I would like to say a word about that. In the United States Pharmacopoeia the term "average dose" is found in the case of almost every drug. Dr. Gold defined "average dose" for you here in the pharmacologic sense. The Pharmacopoeial definition of "average dose" is quite another thing, and I think you may be misled if you do not understand the difference between those two uses of that term. The Pharmacopoeia assigns a dose on the basis of conference between a considerable group of men supposed to be best informed in the case of the particular agent, and on that

basis the committee attempts to pick out a dose which may be stated as the "average dose." It is merely a rough guide to the practicing physician, so that he will have some idea as to the single dose with which he should start the treatment of the patient. I think that the Pharmacopoeial Committee on Therapeutics realizes that the term "average dose" is misused; in fact, I think that they realize that it is an unfair statement, but the physician must have some starting point.

DR. CATTELL: Isn't it usually a minimal dose?

DR. EGGLESTON: It is usually a dose which is, *par excellence*, safe; safe in the sense that it will do no harm. It may not be safe because it may be totally inadequate to accomplish the purpose, and by the time one has discovered this it may be too late to remedy the situation, but the Pharmacopoeia cannot deal with all the problems in a statement such as this. That is all I wanted to say: Keep those two thoughts separate in your minds. The Pharmacopoeial "average dose" is a statement of what is commonly found to be safe, and, presumptively, what a great many physicians believe is more or less effective when repeated. Dr. Gold's use of "average dose" is much more scientific but unfortunately it is one which has not come into vogue as yet with the exception of a few isolated drugs, and those drugs are usually ones with more or less simple actions and reasonably clear-cut end-points for judging their actions.

Dr. Gold also spoke of the question of cumulation in the use of the mercurial diuretics. I don't want to seem to be critical, but I think, possibly, there is another idea there which he omitted to mention, namely, that at times we must consider cumulation of effect as well as cumulation of drug. We know that the mercurial diuretics available to us today do not remain long within the body. Dr. Gold has stated the approximate

period as about twenty-four hours. While it is a fact that, within twenty-four hours, virtually all of the mercurial has been eliminated from the body, there is also the fact that it is often highly undesirable and at times productive of discomfort to the patient to produce dehydration too rapidly. That, perhaps, rather than the danger of toxicity, is one of the explanations for the frequent use of the mercurial diuretics at longer intervals.

DR. CATTELL: I wonder if we might have a few words from Dr. Stewart while we are on this general topic, and then perhaps turn to Dr. Gold for a response.

DR. HAROLD G. STEWART: The diagram that Dr. Gold drew, of the T-wave effect and dosage of digitalis, does not seem to me to have a great deal of relevancy to the therapeutic use of digitalis. I think almost everybody is agreed that you cannot look at a record of a patient who has had digitalis and tell from the T-waves how much digitalis that patient has had. From a therapeutic point of view, I think we do not want the students to carry away the notion that you can look at a record and tell whether a patient is adequately digitalized or not. It may be that if you observed one patient, and repeatedly digitalized him, after allowing time for excretion, that patient, on a certain amount of digitalis might exhibit somewhere near the same kind of T-wave changes; but you cannot predict what another patient would do with the same or another amount of digitalis in the way of T-wave changes. Consequently, we cannot use T-wave effects as a guide to whether we are getting an adequate therapeutic effect from digitalis or not.

To come back to the word "average" again, it seems too bad that there has seeped into the literature a sense that was not made clearly in Dr. Gold's papers about this; it is interpreted by everybody that I have talked to, to mean that if you give 1.2 mg. of digi-

taline Nativelle you digitalize the patient. That is the current notion. I think harm to progress in digitalis therapy has been done by the prevalence of this notion which is now current. As a matter of fact, we see patients now less well digitalized than we did five or six years ago before this notion got around that one could do it with these small amounts. I think in the experience of most people, except Dr. Gold, it takes larger amounts than 1.2 mg. to give adequate digitalization. In our experience here it is somewhere between 1.8 and 2 mg. If 1.2 mg. is the "average" digitalizing dose, it is very unusual that we do not see patients in our experience in whom this amount achieves digitalization.

DR. CATTELL: I am sure there is no disagreement with what Dr. Stewart said with reference to the wide variability among patients in their response to digitalis and the consequent impossibility of using the T-wave or any other criterion to establish the quantity of digitalis administered. It is precisely for this reason that it is so important to have information about individual variability in the population to be treated. We then have advance information on the probability of the average or any other dose giving the desired therapeutic effect, or of its being too large or too small. This is a point of great practical importance which has not been given the attention it deserves. Thus, Dr. Gold's average dose of 1.2 mg. of digitoxin becomes more informative, when at the same time he is able to tell us in what proportion of patients it is ineffective and in what proportion it gives rise to toxic symptoms.

Nothing in what I have just said detracts from the evidence obtained by the comparison of the effects of repeated doses in the same patient. By such means which eliminate the factor of individual variability, it has been established that a definite dosage-response relationship holds and that the

T-wave changes correspond quantitatively to the therapeutic actions.

DR. EGGLESTON: May I raise a point? I quite agree that the studies by Dr. Gold in the attempted establishment of an "average dose" of digitoxin were exceedingly well thought out and very cautiously investigated. I think the use of the term "average dose" without specific definition, conveys the wrong idea to the practicing physician. He certainly generally expects that when he gives the dose set by Dr. Gold, that dose which is quite definitely established as the average, meaning that dose which will produce a given effect in 50 per cent of instances, that it is the therapeutic dose of digitalis. Perhaps it is an unfortunate choice of a word. I do not know what word could have been chosen, but I think that Dr. Stewart is right, namely, that it does convey an erroneous impression. It is all right among our own students here because they understand what is meant by that, but the medical public at large does not.

DR. CATTELL: Do you not still think that if you have the information about the "average dose," it represents the most desirable starting dose?

DR. EGGLESTON: Yes, probably it does. For that matter, I could not help thinking when Dr. Stewart was talking here, and I hope he will pardon me for this remark, that for many years it was routine in this Hospital to give each cardiac patient admitted to the Hospital, without other consideration than that he had not recently been digitalized, 1.8 Gm. of powdered leaf. That is precisely the same principle as Dr. Gold's. We found that 1.8 Gm. of powdered leaf in divided doses was reasonably effective in controlling the majority of the symptoms of congestive heart failure. We were able to save the patients several days of hospitalization by that, and what is still more important, many hours of unnecessary discomfort were saved. However, I think you

ought all to understand that, precise as some procedures are in therapy, there is still the problem that you cannot get away from, namely, that of individual variation of the patient.

DR. CATTELL: If it is safe, may it not be desirable to give more than the average dose which takes care of 50 per cent of the cases? Provided there are no side actions of importance, it would be desirable to give that dose which might encompass the largest number of cases. That can be done with many drugs.

DR. STEWART: I think then, that should be called partial digitalization or some implication of that given.

DR. CATTELL: Now I want to give Dr. Gold a chance to reply.

DR. GOLD: The discussion here establishes the wisdom of the committee in choosing this topic for an airing in the conference today. It just goes to show how little this whole matter is understood. From the standpoint of the Pharmacopoeia, Dr. Eggleston, I would recommend that you and I form a committee of two to urge the Pharmacopoeia to abandon the term "average dose," and substitute the term "the dose" or the "usual dose."

DR. EGGLESTON: That might be well.

DR. GOLD: There is no reason why the Pharmacopoeia, which is so highly scientific in most of its performances, should continue to carry along the term "average" as applied to dosage, in a completely unscientific sense, having it mean not the "average dose," but the dose which the "average physician" prescribes. Please consider the resistance which we are encountering right here at this conference to our endeavor to place the term "average dose" in its proper light. Dr. Stewart and Dr. Eggleston state that it is a source of confusion to physicians because they believe that the term implies that the full effects will be produced in every patient if that dose is given. Perhaps, some do believe that, but I have confidence that the

majority of physicians do not believe that. There is no more mystery about the term "average" as applied to the dosage of a drug than there is to that term applied to the physician's daily income or to the size of men's heads. Clearly, there is need for more education on the subject and for calling attention to the fact that the "average dose" can only produce the desired therapeutic effect in a proportion of the population, a larger proportion in the case of some drugs than of others. The remainder may do with less than the "average dose" or may require more than the "average dose." It is incredible to me that anyone would question the need of determining the true position of the "average dose" in the dosage scale as a basis for deciding what dose should be used as the starting point for therapy. As Dr. Cattell intimated, if it happens to be a drug in which the therapeutic and toxic effects are close, it may be necessary to start treatment in any particular case with less than the "average dose," but if the drug happens to be one in which therapeutic and toxic effects are far apart, treatment may be started in all patients with more than the "average dose." For example, we might determine the "average dose" of penicillin which cures pneumonia, but since penicillin is non-toxic, it would be desirable to treat all patients not with the "average dose," but with a much larger amount, an amount which would cure not 50 per cent of the population, but as close as possible to 100 per cent of the population.

As to the specific example of digitoxin, we published a study in which the term "average full-dose-method of digitalization" was used, and the experience was described in which that turned out to be 1.2 mg. given at one time. Our papers clearly state, and the term "average" clearly implies, that some require more, while others can do with less. Dr. Stewart appears to be taking issue with it, and it is not clear to me whether the

objection is to the conception of the "average dose," or only to the 1.2 mg., or to both.

Since Dr. Stewart stated that "in the experience of most people, except Dr. Gold, it takes larger amounts than 1.2 mg. to give adequate digitalization," I should call your attention to the paper by Stroud and Vander Veer in 1937 in which they found that from 1.2 to 2.0 mg. of digitoxin was necessary for full digitalization when the drug was given over a period of five or six days. There is also the recent paper by Katz and Wise in the American Heart Journal of August, 1945, in which they confirm our results and state that "digitaline 'Nativelle' in 1.2 mg. dosage . . . . would appear to provide safe, effective, single-dose digitalization in undigitalized patients." I believe I know why Dr. Stewart is having so much difficulty with the 1.2 mg. dose. I surmise that he fails to give it at one time, that he does not use the control period which eliminates the effects of rest in bed, as was done in the method by which the 1.2 mg. value was established, and that his experience may not embrace a sufficient variety of grades of failure, from the very mild to the very severe ones. Not dealing with an "average" population, he may fail to observe the expected results of an "average dose."

Dr. Eggleston, your point about the mercurial diuretics is well taken. We all encounter the unpleasant effects of excessive diuresis, and in a case in which it has occurred after the first dose, we have to wait a few days until the patient recovers from them. However, our solution to the problem is not the one you suggest, namely, to spread the interval between injections; it is rather to keep the interval unchanged but reduce the dose. This usually results in a continuous course of improvement or cumulation of effects without the drastic disturbance from excessive single doses given at intervals of four days.

DR. EGGLESTON: I was not discussing the

use of the mercurials. I agree with you that often the individual dose should be smaller.

DR. GOLD: I stated at the beginning that any resemblance of this conference to a discussion on cardiology was purely accidental. I used the frequency distribution curve which we determined for the effect of digitalis on the T-wave of the electrocardiogram as an example of the method which may be used for establishing the "average dose" of a drug and the range of variability in the response of the human population. But since Dr. Stewart has broadened the discussion, I may state that I agree with him that there is no necessary relationship between the T-wave effects of digitalis and its effects in heart failure.

DR. CATTELL: Would you admit that different systems may show different degrees of susceptibility?

DR. GOLD: Indeed I do agree. In point of fact, on the average, it takes about three times as much digitalis to bring about the full therapeutic effects in heart failure as to produce changes in the T-wave, and there are some patients who show negligible changes in the T-wave with doses of the drug sufficient to control heart failure, while others may show advanced T-wave changes with doses of the drug which cause negligible effects in heart failure.

DR. CATTELL: Would you think it safe to apply the frequency distribution curve obtained with the T-wave to the case of treating heart failure?

DR. GOLD: On theoretical grounds, I would hesitate to do so. It could be that the range of variation in the susceptibility of humans from the standpoint of the cure of heart failure might be quite different from that for the T-wave response. The two curves might have different slopes and different lengths. However, as you have already intimated, in the experiments with the T-wave, we found that the "average dose"  $\pm 25$  per cent includes about three-fourths

### Range of Dosage Required for Estrus in the Human

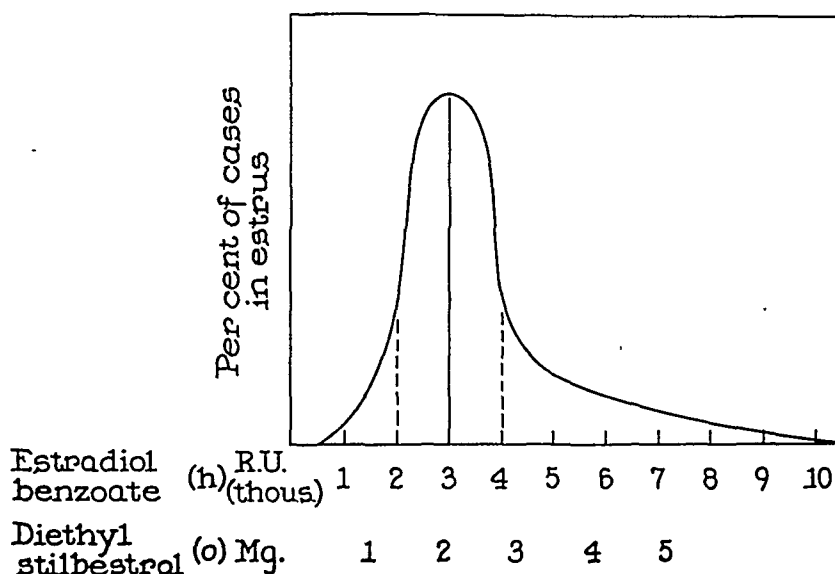


FIG. 3.

of the population, and in our experiments with heart failure and auricular fibrillation, the single dose of 1.2 mg. of digitoxin given at one time, as well as the 0.2 mg. given daily for maintenance, produce satisfactory digitalization and maintenance respectively, also in approximately three-fourths of the population. The results, therefore, suggest that in the case of these two responses to digitoxin, the two curves happen to be similar.

DR. EPHRAIM SHORR: Everything that Dr. Gold has said about dosage in cardiology has occurred to every one of us who, in our respective fields, have been concerned with therapeutic misinterpretations of the same character; and I am sure that each one of us could cite example after example that fit each of the fundamental therapeutic principles which Dr. Gold has so well laid down. The field of endocrinology is probably surrounded by more therapeutic pitfalls than almost any other that I could name. Let us, for example, consider the use of estrogens. We have been provided with a number of potent estrogenic preparations which are standardized in terms of rat units

or international units. There is an average dosage suggested by the Pharmacopoeia. This average dosage is arrived at in the same way as the average dose of other drugs and is equally useless as a guide for therapy. The bio-assay of these materials is carried out on the same principles as that for other drugs, namely, a 50 per cent response. The chief purpose of this assay is to insure that estrogenic preparations meet standard requirements. However, their direct application to therapy in the human must, in order to be successful, be guided by the fundamental therapeutic principles which hold for any other drug and by the recognition that gross individual variations in responsiveness exist in the human population as in the rat colony on which the bio-assays have been made. It is, therefore, essential that we have some objective index analogous to the T-wave in the electrocardiogram to serve as a guide post. For the estrogenic hormones this is provided by the vaginal smear which undergoes specific cytological alterations under the influence of estrogens, its end-point being a fully cornified smear. When one uses this index as a basis for replacement therapy



with estrogenic hormones one finds the expected variation in dosage requirements from patient to patient. This range of dosage is shown semi-diagrammatically in Figure 3. It is, of course, possible to select a range of dosage which will put approximately 50 per cent of patients in full estrus; however, this dose will be excessive for a certain percentage of patients and inadequate for another group. This circumstance is completely analogous to the response to the average digitalizing dose of digitoxin as Dr. Gold has pointed out.

A second variable in the use of the estrogenic hormones is presented by variations in the intervals between injections. Thus, you may get entirely different results using any given total dose depending upon whether the whole amount is given at wide intervals, or in divided doses given daily. By far the most efficient utilization of the hormone occurs when it is given daily. Finally, there is the matter of the cumulative effect of estrogens. If a dose is inadequate to achieve a desired effect it may be given indefinitely without fulfilling its purpose.

I am sure that these three examples which illustrate the relevance of Dr. Gold's discussion of the fundamental principles which should guide therapy could be multiplied indefinitely, not only in the field of endocrine therapy, but in virtually all of the medical disciplines.

#### SUMMARY

DR. GOLD: The discussion in the conference this afternoon centered on problems

of dosage. The principles were explored and illustrated by examples from a wide variety of drugs. There are two systems of dosage by which drugs are administered, the cumulative and the non-cumulative systems, and for their most effective application, use must be made of pharmacologic facts relating to speed of absorption and elimination. The mechanisms of these systems were described. The significance of the "average dose" was discussed, and a method for establishing the "average dose" in humans was outlined. The "average dose" of digitalis received special attention. It was stated by one participant that the "average dose" with respect to the effect of digitalis on the T-waves of the electrocardiogram bears no relation to the average therapeutic dose of the drug, while others presented evidence indicating a close correlation between the two types of endpoints.

It was stated that the position of the "average dose" is not known in the case of most drugs, and that the term "average dose" is incorrectly applied to the dose which the "average physician" prescribes. The application of the principles of dosage was considered in relation to such common therapeutic agents as digitalis, epinephrine, neostigmine, phenobarbital, picrotoxin, morphine, quinidine, mercurial diuretics and estrogenic hormones. It was pointed out that if physicians were to make more systematic use of the basic principles of dosage plans, the efficacy of drug therapy would greatly increase.

# Clinico-pathological Conference

## Blood Dyscrasia with Cardiac Complications\*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. W., was a sixty-one-year old white divorced bank guard, who entered the Barnes Hospital for the first time on October 9, 1946, complaining of shortness of breath. The family history was non-contributory. The past history revealed that the patient had had pneumonia in 1914 without complications. He had had no other serious illnesses, and the systemic review was negative.

Approximately one year before entry, the patient was told by friends that his eyes were becoming more prominent and from that time on exophthalmos had increased. Shortly after the prominence of his eyes was first noted, the patient became more nervous and developed a slight tremor of his hands. About four and one-half months prior to admission, he became dyspneic for the first time on exertion; dyspnea increased rapidly so that soon it was present when the patient was at rest. Orthopnea and a persistent, non-productive cough occurred. Concomitantly the patient became aware of masses in his neck and in the axillae, and he entered the Washington University Clinics.

There it was recorded that he did not look particularly ill. A patchy maculopapular erythematous eruption was noted over the chest and inguinal regions. There was generalized lymphadenopathy; the nodes varied from  $\frac{1}{2}$  to 2 cm. in diameter and were discrete, firm and non-tender. The eyes were prominent. The pupils reacted to light and

accommodation and extra-ocular movements were normal. The optic fundi showed only moderate retinal sclerosis; no hemorrhages or exudates were present. The tonsils were enlarged but did not appear inflamed. The lungs were clear to percussion and auscultation. The left border of cardiac dullness was 9 cm. to the left of the midsternal line in the fifth interspace. The rhythm was regular, the sounds were of good quality and there were no murmurs. The spleen was palpable 10 cm. below the left costal margin but the liver edge could not be felt. The prostate was twice its normal size. There was no clubbing or edema and the neurologic examination was within normal limits. Laboratory studies included a normal red blood count and hemoglobin. The white cell count was 173,550 and the differential count showed 1 per cent stab form, 3 per cent segmented forms, and 96 per cent lymphocytes; 6 per cent of the lymphocytes were immature. A chest film was read as follows: "The cardiac silhouette is within normal limits. The hilar markings are prominent on both sides. There is pulmonary infiltration in the second and third anterior interspaces on the right and to a lesser extent along the descending bronchi. X-ray diagnosis: peribronchial infiltration of an indeterminate nature."

A diagnosis of chronic lymphatic leukemia was made and from June 26, 1946, to July 31, 1946, the patient was given

\* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.

seventeen x-ray exposures. He was then followed in the Anemia Clinic where examination revealed that the spleen and lymph nodes were reduced in size. On September 17, 1946, the following laboratory data were recorded: red blood count, 4,480,000; hemoglobin, 13.2 Gm.; reticulocyte count, 3 per cent; white cell count, 37,400; differential count: 1 per cent eosinophiles, 1 per cent segmented forms, 96 per cent lymphocytes, and 2 per cent monocytes; platelets, 270,000.

During the course of x-ray therapy most of the patient's symptoms had improved considerably but his appetite became poorer. He felt fairly well until one week prior to entry when he again became markedly short of breath and developed nausea, vomiting and diarrhea. Six days before admission he complained of pain in the left chest substernally, associated with marked orthopnea. Three days before admission edema of the legs appeared. Because of the persistence of these symptoms he was admitted to the hospital.

No temperature reading was recorded and the pulse was not obtainable. The respirations were 32 per minute and shallow, and the blood pressure was 85/65. The patient was critically ill and sat on the edge of the bed gasping for air. The arms and legs were cold and clammy and there was cyanosis of the lips and of the finger nail beds. Moderate exophthalmos and lid lag were noted. The mucous membranes of the mouth were cyanotic. The tongue protruded in the midline without tremor. There was marked distention of the neck veins. The trachea was in the midline; the thyroid was normal in size but a small nodule was palpated in each lobe. There was dullness to percussion at the base of the right lung and over this area tactile fremitus, breath sounds and spoken voice were diminished. No râles were heard and the remainder of the lung fields was clear to percussion and auscultation. The cardiac impulse could not

be seen or felt and no heart sounds were audible. The heart was enormously enlarged; right border dullness was 3 cm. from the midsternal line in the second interspace, 5 cm. in the third interspace, 9 cm. in the fourth interspace, and 13 cm. in the fifth interspace. The left border of cardiac dullness was 6 cm. to the left of the midsternal line in the second interspace, 8 cm. in the third, 12 cm. in the fourth, and 16 cm. in the fifth interspace. The spleen was palpable 7 cm. below the left costal margin, and the liver 11 cm. below the right costal margin. There was 4+ pitting edema of the feet and lower legs.

The laboratory findings were as follows: Red cell count, 4,550,000; white cell count, 96,000; differential count: 8 per cent segmented forms, 92 per cent lymphocytes. Blood Kahn reaction: negative. Venous pressure: 310 mm. NaCl. Circulation (arm to tongue with Decholin): 78 seconds. Roentgenogram of the chest: "The cardiac silhouette is enlarged to the right and left. The hilar shadows are prominent and there is fluid in the right pleural cavity." An electrocardiogram revealed low voltage in leads I, II and III, moderate slurring of all ventricular complexes, inversion of the principal component in I with upright principal components in II and III. There was a Q wave in CF<sub>IV</sub>. Interpretation: "right bundle branch block and low voltage."

Immediately on entry the patient was given oxygen through a positive pressure mask and his cyanosis was relieved; however, he could not tolerate the mask and it had to be removed. Because the signs were thought to be those of cardiac tamponade, pericardial paracentesis was attempted; a No. 18 needle was introduced in the left fifth interspace at the outer border of cardiac dullness. No resistance was met and after the needle had penetrated 4 cm. blood was easily aspirated. Fifty cc. were withdrawn and the procedure was terminated. The

patient tolerated it well. The count on the bloody fluid obtained revealed 4,810,000 red cells, 13 Gm. of hemoglobin and 80,600 white cells. As a result of these findings it was concluded that the patient had acute cardiac dilatation rather than cardiac tamponade and he was given 1.6 mg. of lanatoside C intravenously over a period of five minutes. Shortly after the injection was completed, he slipped backward from his sitting position, had a mild generalized convulsion, took a few deep gasps for breath and expired. Death occurred approximately one and one-half hours after admission.

#### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Two features of this case deserve discussion, namely, the hematologic diagnosis and the etiology of the heart disease. Because the patient died so soon after admission to the hospital, the data are somewhat limited. Dr. Moore, would you comment on the hematologic problem?

DR. CARL V. MOORE: This patient probably had chronic lymphatic leukemia. I qualify my statement because neither a lymph node biopsy nor a bone marrow aspiration was recorded, and rarely a leukemoid reaction, characterized by a great increase in cells of the lymphatic series, may result from a chronic infection such as tuberculosis or from wide-spread neoplastic disease.

DR. ALEXANDER: Could lymphosarcoma be associated with a peripheral blood picture such as that seen in this case?

DR. C. V. MOORE: Yes, but I believe it can be excluded here. As you know, there is considerable interest among members of the hematologic division in the occurrence in lymphosarcoma of a peripheral blood picture simulating that of lymphatic leukemia. Not one of the members of the division who examined this patient's

smear thought that the cells were those of lymphosarcoma.

DR. ALEXANDER: Is it true that x-ray therapy may lead to the development of a leukemoid peripheral blood picture in lymphosarcoma?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: Does pulmonary infiltration occur in leukemia?

DR. ALFRED GOLDMAN: It is seen not infrequently. I do not believe that the x-ray findings in this case are necessarily due to infiltration with leukemic cells however; they may have represented the changes of low grade pneumonitis.

DR. ALEXANDER: Is it possible to distinguish Hodgkin's disease from leukemia by the nature of the pulmonary infiltration?

DR. C. V. MOORE: I do not think so. In general, approximately one-third of patients with lymphosarcoma, Hodgkin's disease, and chronic lymphatic leukemia have some form of pulmonary involvement equally divided between pulmonary infiltration, mediastinal adenopathy and pleural effusion. Given one of these changes, however, I do not believe that the correct hematologic diagnosis can be made on the basis of the x-ray film.

DR. ALEXANDER: This patient received seventeen x-ray treatments and it was noted that the size of the spleen diminished. Are the cells of lymphatic leukemia quite sensitive to roentgenotherapy?

DR. EDWARD H. REINHARD: They are definitely radio-sensitive although not to as great a degree as the cells of leukosarcoma.

DR. ALEXANDER: Apparently the pulmonary infiltration cleared after x-ray therapy. Would you have expected the spleen to return to normal size?

DR. REINHARD: Usually there is a greater decrease in the size of the spleen than was noted in this case. However, the response to x-ray therapy depends to a considerable extent on the duration of splenic enlarge-

ment; the longer the spleen has been enlarged, the less likely is there to be a good response to x-ray therapy.

DR. DONALD S. BOTTOM: It should be pointed out that this patient did not receive x-ray therapy directly to the spleen but only to the inguinal, axillary and cervical nodes. Frequently, however, the spleen is reduced in size even though radiation is not directed toward it.

DR. ALEXANDER: If x-ray therapy was directed primarily to the spleen, would the lymph nodes be expected to decrease in size?

DR. BOTTOM: Occasionally such a response is seen.

DR. ALEXANDER: What has been your experience, Dr. Reinhard, in this regard?

DR. REINHARD: I agree with Dr. Bottom. If x-ray is directed to large lymph nodes, they will decrease more rapidly and to a greater extent than if the therapy is directed, for example, to the abdomen, but they usually decrease to some extent even if they are not subjected to direct radiation.

DR. ALEXANDER: You have used radio-active phosphorus in a large number of cases. Do you feel that it should have been used in this patient?

DR. REINHARD: Radio-active phosphorus could have been used, but if reduction in the size of specific lymph nodes or the spleen is the prime objective of therapy, x-ray is preferable.

DR. ALEXANDER: Would you comment on the use of other isotopes?

DR. REINHARD: With the information available to date, I do not believe that any other isotopes have any real advantage over x-ray therapy or radio-active phosphorus.

DR. ALEXANDER: Would you comment on the duration of lymphatic leukemia. Does the prognosis vary with age?

DR. REINHARD: In general, the course of chronic lymphatic leukemia in older patients is more benign than it is in patients in

the younger age group. The former are more likely to have evidence of the disease as indicated by peripheral lymphadenopathy for a considerable period of time before general systemic effects are noted, and after the diagnosis is made, the older patients survive for a longer period of time. The average duration of life in patients between the ages of twenty and fifty is approximately three years. In a patient over sixty the predicted duration is about four years.

DR. ALEXANDER: Would you comment on the duration of life in myelogenous leukemia?

DR. REINHARD: With the most successful treatment the average course of the disease covers three and one-half years; without treatment the duration is three years. It is important, however, to emphasize that adequate therapy increases the period of useful activity greatly; that is, the patients remain essentially symptom-free until very near the time of death.

DR. C. V. MOORE: I think that Dr. Reinhard's estimate for the average duration of life in myelogenous leukemia was too short. Patients with myelogenous leukemia may live for ten years; this summer Dr. John Lawrence told me that in his experience the average duration of life for patients with myelogenous leukemia, treated with radio-active phosphorus is now over four and one-half years and he thinks that ultimately such patients may be expected to survive for more than five years.

DR. REINHARD: My estimate was based on results in patients with both acute and chronic myelogenous leukemia.

DR. ALEXANDER: Dr. Moore, would you comment on chronic lymphatic leukemia occurring late in life.

DR. C. V. MOORE: Patients with chronic lymphatic leukemia may live for twenty years; such instances are the exception rather than the rule. Dr. Lawrence's

statistics for duration of life in chronic lymphatic leukemia averaged about six years; our results have not been so favorable.

DR. ALEXANDER: Approximately four and one-half months before his death, this man noted dyspnea on exertion and soon thereafter became orthopneic. Dr. Smith, do you believe that these symptoms arose because of cardiac insufficiency?

DR. JOHN R. SMITH: Certainly cardiac disease is the most common cause of dyspnea and orthopnea.

DR. ALEXANDER: When the patient was examined in the clinic, his heart was not enlarged, the sounds were of good quality and there were no murmurs. Unfortunately no blood pressure reading was recorded. The chest x-ray showed no cardiac enlargement. Do you think those findings are compatible with a cardiac basis for the dyspnea and orthopnea?

DR. SMITH: Yes.

DR. ALEXANDER: With x-ray therapy, apparently all of the patient's symptoms improved and he did fairly well until one week before death when he had substernal distress and a rapid progression of the cardiac symptoms—dyspnea, orthopnea and edema. Dr. Massie, what is your interpretation of that sequence of events.

DR. EDWARD MASSIE: Two possible causes for the symptoms seem plausible; either the patient had a myocardial infarction or he developed a pericardial effusion.

DR. ALEXANDER: Do you believe that the dyspnea and orthopnea which the patient had before he received x-ray therapy were suggestive of cardiac insufficiency.

DR. MASSIE: No, I believe that they more likely were based on an extracardiac factor.

DR. ALEXANDER: What extracardiac causes would you consider?

DR. MASSIE: Either pulmonary infiltration or severe anemia could have been responsible for the symptoms. In this case

the anemia was only slight and therefore I would consider pulmonary infiltration as the major factor.

DR. ALEXANDER: Do you believe that the x-ray film indicated sufficient pulmonary infiltration to give rise to dyspnea and orthopnea?

DR. MASSIE: No, I do not. However, I have seen, on occasion, patients who presented themselves because of dyspnea and orthopnea and although careful study revealed no cardiac cause of the symptoms, eventually a blood dyscrasia was uncovered as the basis of the symptoms.

DR. ALEXANDER: Dr. Moore, what is your experience?

DR. C. V. MOORE: Dyspnea and orthopnea on the basis of pulmonary infiltration is rare, even in cases in which there is also marked involvement of the mediastinum.

DR. REINHARD: I agree with Dr. Moore. It should be pointed out, however, that in lymphatic leukemia the myocardium may be heavily infiltrated with abnormal cells.

DR. ALEXANDER: Do you believe that the patient improved after his x-ray therapy because of the destruction of abnormal cells in the myocardium.

DR. REINHARD: I do not know.

DR. ROBERT A. MOORE: Heavy pulmonary infiltration in blood dyscrasias is rare. Likewise infiltration of the myocardium to a marked degree is not common. Infiltration of the endocardium with abnormal cells, however, is a common manifestation of leukemia.

DR. ALEXANDER: Dr. Massie, is bundle branch block usually attributed to coronary-artery disease?

DR. MASSIE: Yes. In this case, however, the pain in the left chest may have been associated with pericarditis or pericardial effusion rather than with coronary insufficiency. The bundle branch block may have been existent for many years and its presence in a single electrocardiogram would not

allow one to differentiate between coronary-artery disease and pericardial disease as the cause of the chest pain.

DR. ALEXANDER: This patient developed progressive exophthalmos and a tremor of the hands; on physical examination a nodule was felt in either lobe of his thyroid. No basal metabolic rate was recorded. Dr. Futcher, do you believe that histologic evidence of hyperthyroidism will be found by the pathologists?

DR. PALMER H. FUTCHER: It has been pointed out frequently that the symptoms of hyperthyroidism are often present in leukemia. It has been suggested by one writer that thyrotoxicosis and leukemia both may arise from stimulation of the sympathetic nervous system and he has treated leukemic patients with iodine in the hope of controlling the course of the disease. I should like to ask Dr. Moore how often a hyperplastic thyroid is found in leukemia.

DR. C. V. MOORE: I cannot answer that question, Dr. Futcher. I have always assumed that the increased metabolic rate in leukemia was related to the number of abnormal cells circulating rather than to the thyroid gland *per se*.

DR. ALEXANDER: The question arises as to whether this patient had a bloody pericardial effusion. The physical signs were classical of those seen in pericardial effusion.

DR. MASSIE: I agree that blood was probably present in the pericardium.

DR. FUTCHER: I believe that a more likely explanation is that the needle was in the ventricle.

DR. ROBERT J. GLASER: When we saw this patient, the clinical picture was thought compatible with pericardial effusion and cardiac tamponade, and because of the patient's critical condition, pericardial paracentesis was considered justified. The needle was inserted very slowly but at no time was resistance encountered to suggest that the needle had pierced the ventricular muscle.

As soon as bloody fluid was obtained, the procedure was terminated and cell counts were done. The counts indicated that pure blood had been withdrawn.

DR. ALEXANDER: Are there possibilities other than that the ventricular cavity was entered?

DR. W. BARRY WOOD, JR.: Rupture of the auricle or ventricle could explain a bloody pericardial effusion.

DR. ALEXANDER: Yes, the patient may have had a myocardial infarction one week before entry when he first complained of substernal pain with subsequent rupture at the site of infarction.

DR. WOOD: It is also possible that there was pericardial infiltration by leukemic cells with a secondary bloody effusion. Such a finding is not uncommon when carcinoma extends to the pericardial sac.

DR. ALEXANDER: Dr. Moore, is pericardial infiltration and a bloody pericardial effusion common in leukemia?

DR. C. V. MOORE: I do not know, Dr. Alexander. However, Dr. John Tinsley told me of a case report describing infiltration of the auricular wall in leukemia with subsequent rupture and cardiac tamponade. In another case the aortic wall was infiltrated with leukemic cells and subsequently ruptured.

DR. ALEXANDER: It is said that invasion of the pericardium by lymphomas is rare.

DR. R. A. MOORE: I have seen it in a few cases, and in some of these, bloody pericardial fluid was present.

DR. ALEXANDER: The physical findings certainly suggested a pericardial effusion. The heart was tremendous and the signs were classical.

DR. C. V. MOORE: Dr. Robert Moore mentioned that lymphomas may involve the pericardium. I have seen that happen with lymphosarcoma or with Hodgkin's disease, but I do not understand its occur-

rence in lymphatic leukemia. Pleural effusion and ascites are not uncommon in lymphatic leukemia and yet in such instances involvement of the serous membrane with abnormal cells is not found.

DR. R. A. MOORE: I was speaking primarily of lymphosarcoma but occasionally pericardial involvement is seen with leukemia.

DR. GLASER: I should like to justify the use of lanatoside C here. Because of the character of the fluid obtained on pericardial tap, it was concluded that the patient had cardiac dilatation rather than pericardial effusion, and because nothing else seemed to offer any hope, rapid digitalization was attempted.

DR. WOOD: The decision to digitalize this patient was motivated somewhat by a previous experience in which a similar problem faced the staff when a pericardial tap was attempted and blood was obtained. A diagnosis of cardiac dilatation was made in that instance, the patient was digitalized and responded dramatically. It was believed in the present case that digitalis should not be withheld. If the diagnosis of pericardial effusion could have been substantiated, lanatoside C would not have been given.

DR. ALEXANDER: In summary, it is clear that this patient had chronic lymphatic leukemia. The etiology of his heart disease cannot be definitely established; pericardial effusion is apparently ruled out leaving as the most likely possibility coronary artery disease or thyrotoxic heart disease. The patient very possibly had thyrotoxicosis although, as has been pointed out, leukemia and thyrotoxicosis have certain clinical features in common.

**CLINICAL DIAGNOSIS:** Chronic lymphatic leukemia and cardiac insufficiency due to either coronary artery sclerosis or thyrotoxic heart disease complicating hyperthyroidism.

#### PATHOLOGIC DISCUSSION

DR. FRANK VELLIOS: At the time of autopsy, the veins of the face and neck were markedly distended and there was edema of the lower extremities. One thousand cc. of fluid were present in the peritoneal cavity, 150 cc. in the right pleural cavity and 300 cc. in the left pleural cavity. The pericardial sac contained 50 cc. of serosanguineous fluid. The heart weighed 700 Gm. and was large, pale and flabby. Near the tip of the left ventricle there was a needle puncture which extended into the cavity. All four chambers were greatly dilated but the ventricular walls were not particularly thickened. The right ventricle measured 5 mm. in thickness, the left, 14 mm. The coronary arteries showed a few arteriosclerotic plaques but none of these encroached upon the lumina of the vessels. The thyroid gland weighed 28 Gm. A small, firm, encapsulated nodule was present in the left lobe; in the right lobe there was a cyst, 1.5 cm. in diameter, containing yellow material. The lungs weighed 2,300 Gm. and were large and firm. The liver weighed 2500 Gm. and was large, firm and purple in color. The spleen, which weighed 900 Gm., was firm and red. The kidneys were not remarkable. Petechiae and ecchymoses were present in the serous membranes.

DR. R. A. MOORE: To answer the questions outlined in the discussion, let us first consider the problem of the hematologic disease. On the basis of the gross observation of enlarged lymph nodes, splenomegaly, hepatomegaly, petechiae and ecchymoses in a number of organs, the diagnosis of chronic lymphatic leukemia can be confirmed.

To turn to the cardiac disease, it was noted that the heart was hypertrophied and dilated. Either valvular disease or hypertension could have explained the heart findings but the absence of changes in



the kidneys would effectively rule out the latter and no valvular abnormalities were noted. The 50 cc. of pericardial fluid was slightly blood-tinged, but other than the identification of the site of the needle puncture in the ventricular wall, there was no evidence of any significant sequelae of the pericardial paracentesis. Attention should be called to the fact that in the laboratory ventricular puncture is a common procedure which is almost always innocuous.

During the clinical discussion the question as to whether the pulmonary infiltration was responsible for the cardiac symptoms was raised, but this explanation must be rejected because the hypertrophy and dilatation involved not only the right ventricle but also the left, and indeed the left ventricular involvement was more marked. No lesion was found in the lung either grossly or microscopically to have accounted for the cardiac symptoms. The amount of coronary artery disease was insignificant. Only a few plaques were found in the vessels and these did not significantly impinge on the lumina. Anemia should be considered as an explanation for dilatation and hypertrophy of the heart, for 50 per cent of patients with pernicious anemia exhibit hypertrophy of the myocardium without apparent cause other than the anemia. In such instances, however, fatty degeneration is found and the classical "tigered" papillary muscles are seen. Another possible cause of cardiac disease is the lesion called Fiedler's myocarditis or isolated myocarditis. These diagnoses must be based on microscopic findings and will be considered subsequently. One must consider the possibility of thyrotoxic heart disease in view of the presence of an adenoma in the thyroid gland. The lesions noted in the gross, however, would not be expected on microscopic study to give evidence of thyrotoxico-

sis. The histopathologist finds it difficult to correlate gross and microscopic findings in such an instance as this. Other improbable causes of the cardiac findings include so-called beriberi heart and radiation effect. When a sufficient dose of radiant energy is directed to the heart, the myocardium may be injured and feasibly such changes might lead to dilatation and hypertrophy. This patient, however, did not receive radiation to the cardiac area and that possibility must be excluded.

DR. WOOD: Would you comment on leukemic infiltration of the myocardium as a cause for hypertrophy and dilatation of the heart?

DR. R. A. MOORE: The microscopic sections did not show any such infiltration. Figure 1 shows a section of the capsule of a lymph node. The lymphoid tissue is depleted and the cells, which are all of the lymphoid series, may be identified as leukemic cells. There is infiltration in the capsule and in the perilymphatic fat. A section of the lymph node (Fig. 2) shows total destruction of the normal architectural pattern. The cells are all small and uniform in appearance and thus are typical of those seen in chronic lymphatic leukemia.

In the next section (Fig. 3), taken from the bone marrow, there are a few foci of active erythropoiesis but most of the marrow is occupied by leukemic cells of the lymphoid type; there is a decrease in the number of myeloid elements. In Figure 4, a section of the bone marrow under higher magnification shows typical small lymphocytes. The next section (Fig. 5) is from the liver and shows a small amount of leukemic infiltration in the portal spaces and passive congestion of the central areas. The sinusoids are greatly dilated and there is compression and necrosis of the liver cells in the central portions of the lobules. Figure 6 is from the spleen and shows a large follicle. The white pulp is markedly increased in

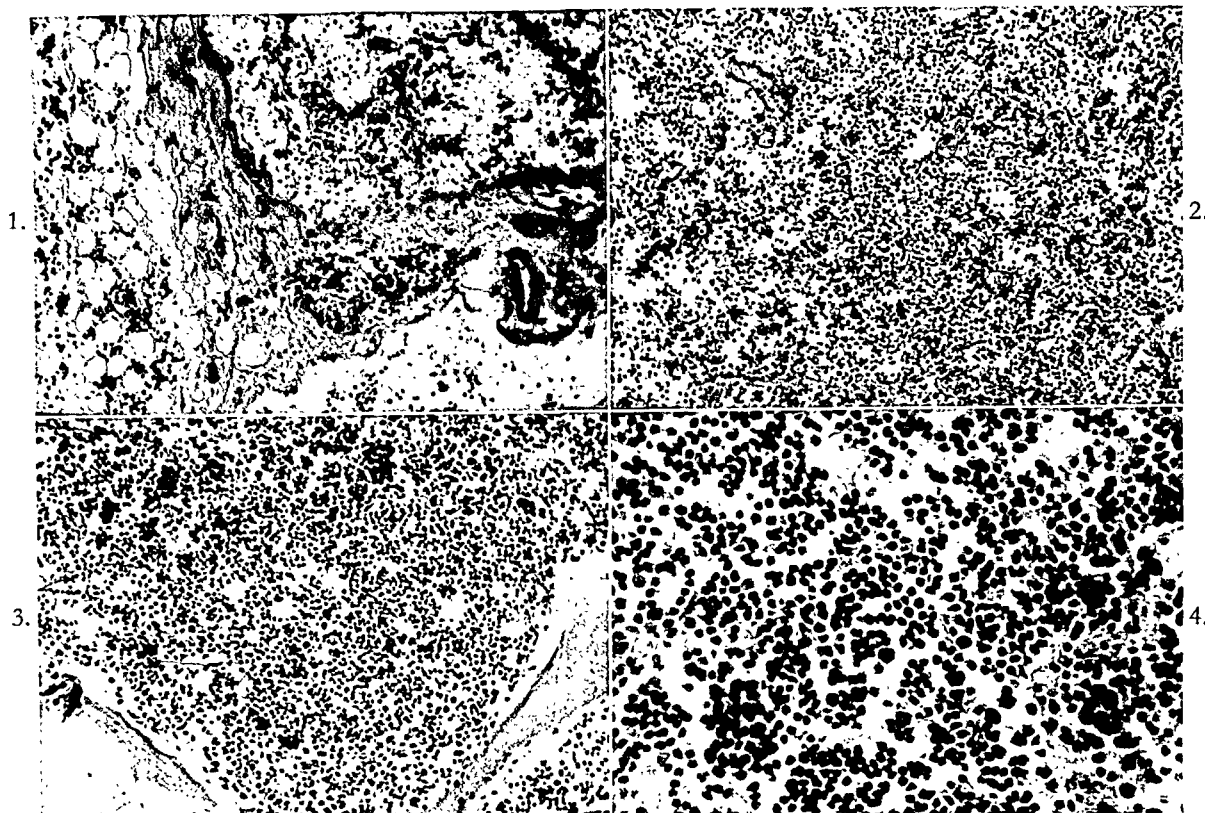


FIG. 1. Section of the periphery of a lymph node showing infiltration of the perilymphatic fat with leukemic cells.  $\times 47$ .

FIG. 2. Section of the same lymph node showing destruction of the normal architectural pattern by leukemic cells.  $\times 47$ .

FIG. 3. Section of bone marrow which shows leukemic infiltration.  $\times 47$ .

FIG. 4. High power view of same section seen in Figure 3. There are a few foci of erythropoiesis but leukemic cells predominate.  $\times 100$ .

amount because of the presence of leukemic cells and there is a relative decrease in the red pulp. From these microscopic sections the diagnosis of chronic lymphatic leukemia can be substantiated, and from an anatomic standpoint the disease would appear to have been under good control at the time of death for infiltration into the various organs was not massive.

In a section of the thyroid gland (Fig. 7), it is noted that the cells are cuboidal or flat, but the tall columnar cells, which are usually but not invariably associated with hyperthyroidism, are not seen. Occasionally cuboidal cells apparently are present in hyperthyroidism. There is no totally satisfactory method of correlating the clinical picture with the histologic findings in

the thyroid gland. A section from the edge of the adenoma (Fig. 8) shows a number of small acini which are relatively free of colloid and it is seen that the acini are apparently isolated in rather acellular interstitial tissue. These are the characteristics of a fetal adenoma. There is no way to decide definitely whether or not the adenoma was toxic.

Figure 9 shows a typical section from the myocardium. The appearance suggests old destruction of some of the myocardial fibers and there is an actual increase in the amount of interstitial tissue. In the next section (Fig. 10) another region is seen in which edema and recent hemorrhage into the tissue are conspicuous. Whether these findings can be attributed to the digitalis

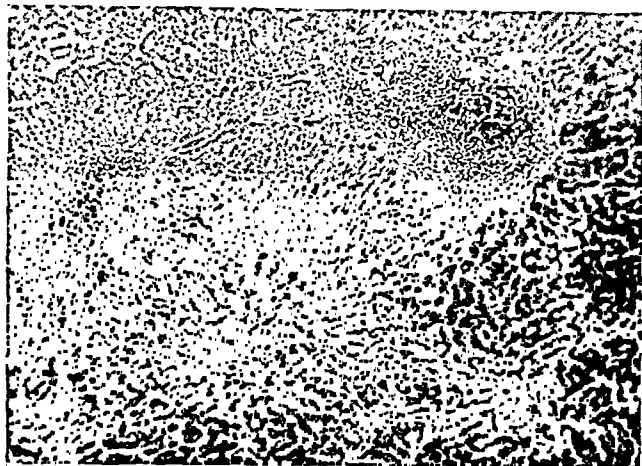


FIG. 5. Section of the liver which shows leukemic cells in the portal spaces and central necrosis.  $\times 47$ .

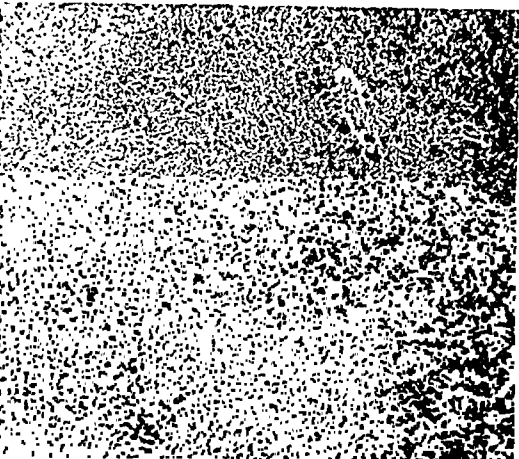
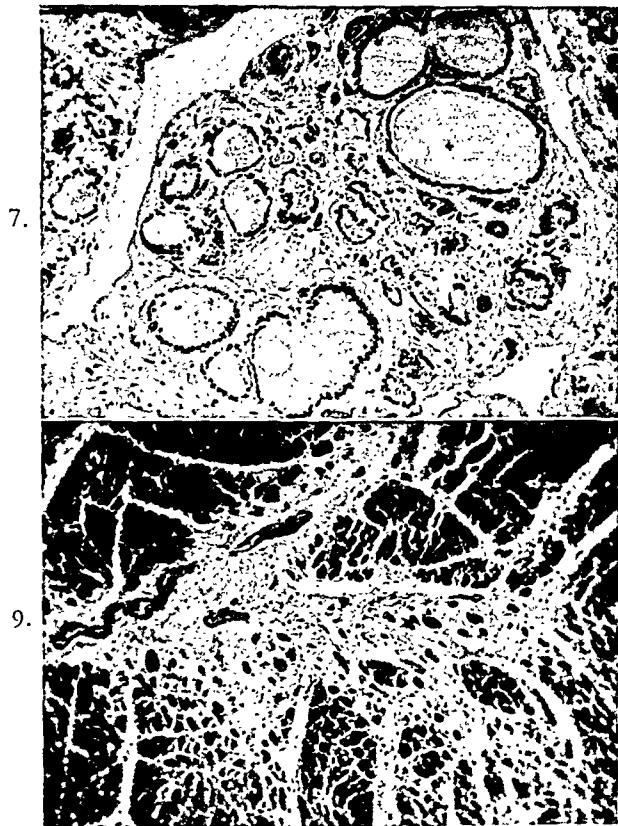
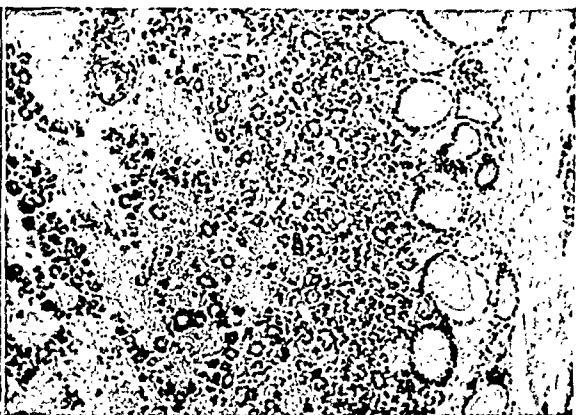


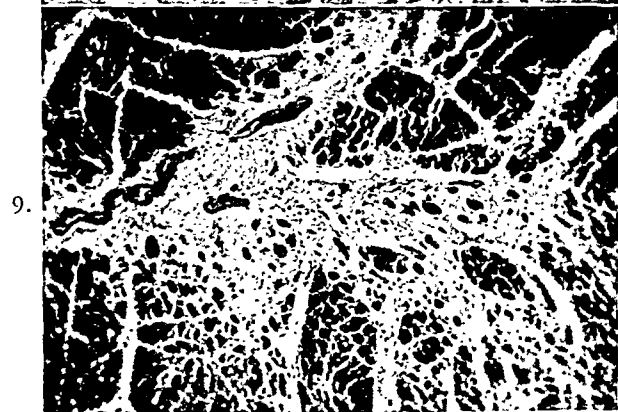
FIG. 6. Section of the spleen showing characteristic changes of chronic lymphoid leukemia.  $\times 47$ .



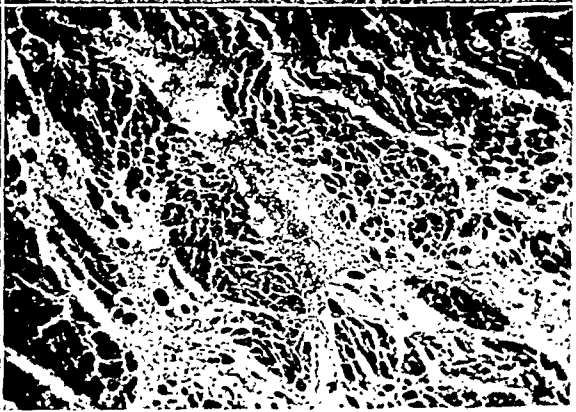
7.



8.



9.



10.

FIG. 7. Section of thyroid gland. No tall columnar cells are apparent.  $\times 47$ .

FIG. 8. Section from the fetal adenoma of the thyroid. The acini are small and contain little colloid.  $\times 47$ .

FIG. 9. Section of the myocardium showing increase in the amount of interstitial tissue.  $\times 47$ .

FIG. 10. Another section of the myocardium which shows edema and hemorrhage.  $\times 47$ .

glycoside cannot be stated. Occasionally such lesions are noted in the heart muscle of patients who have received a large amount of digitalis.

Returning to the differential diagnosis, many of the suggested possibilities must be excluded on the basis of the microscopic findings. Fiedler's myocarditis is characterized by considerable cellular infiltration, usually lymphocytes and eosinophiles, and such a diagnosis is not tenable here. Had a basal metabolic rate been determined, the existence of thyrotoxic heart disease could better have been established. It is true that in hyperthyroidism destruction and fibrous replacement in the myocardium is seen. Radiation effect and beriberi heart disease seem very unlikely.

DR. WOOD: It was recently brought to my attention that investigation by radiologists has indicated that the myocardium is one of the most radio-resistant organs in the body and that the amount of x-ray necessary to cause myocardial damage is tremendous. For this reason it would appear to me that a diagnosis of thyroid heart disease is much more likely in this case.

DR. R. A. MOORE: Unfortunately, the diagnosis of thyrotoxic heart disease cannot be made without qualification, but it is certainly suggested by a process of elimination.

DR. WOOD: In thyrotoxicosis there is stimulation of the entire lymphatic system which is well recognized clinically. The possibility that the onset of the patient's lymphatic leukemia may have had some relation to the thyrotoxicosis must be

considered. Dr. Moore, would you comment on this possibility.

DR. C. V. MOORE: The possible relationship of lymphatic leukemia and thyrotoxicosis has been mentioned in the discussion, and it is true that on occasion total removal of the thyroid has been done in an attempt to alter the course of lymphatic leukemia. The operation has never been successful, however, and more recently the treatment of lymphatic leukemia with thiouracil has not been of value.

DR. FUTCHER: Differential diagnosis of arteriosclerotic and thyroid disease is often difficult and whenever a patient has cardiac enlargement, the basal metabolic rate should be determined.

DR. REINHARD: In this instance a basal metabolic rate would not have been particularly helpful since a reading of +40 to +60 could easily have been attributed to the leukemia.

DR. R. A. MOORE: In summary, from the gross and microscopic findings in this case, the diagnosis of chronic lymphoid leukemia is confirmed; the disease was well controlled at the time when the patient died. Although hyperthyroidism and associated thyrotoxic heart disease cannot be established without equivocation, the anatomic findings are compatible with those diagnoses.

*Final Anatomical Diagnoses:* Chronic lymphoid leukemia; fetal adenoma and cyst of the thyroid; hypertrophy and dilatation of the heart; chronic passive congestion of the lungs, liver and spleen; hydrothorax, bilateral, and ascites.

# Case Report

## Permanent Heart Block Following German Measles\*

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CARDIAC complications of German measles are rare. In a review of sixty-six years of medical literature, we were unable to find a report of a case of permanent auriculoventricular heart block following German measles. Temporary heart block following German measles and measles has been reported.<sup>1,2,3</sup> We are reporting a case of auriculoventricular heart block discovered by electrocardiographic examination in a previously healthy young physician three weeks after an attack of German measles. The permanency of the block permitted studies of the effects of prostigmin, atropine and quinidine upon the electrocardiographic pattern.

### CASE REPORT

A physician, aged twenty-six years, was examined on December 1, 1944, complaining of a rash on the neck and chest, sore throat, and tender nodes in the occipital area, and in the lateral and posterior regions of the neck, all of which had been present for two days.

The history revealed no previous illness, excepting an occasional upper respiratory infection. Examination revealed a generalized papular and morbilliform rash of the neck and chest, slight pharyngitis, and tender lymphadenopathy of the mastoid, cervical and occipital regions. The temperature was 99.6°F., the pulse rate was 88 per minute, and the blood pressure was 122/78. There were no abnormal physical findings; there were no detectable abnormalities of the heart and there were no Koplik spots.

The laboratory examination revealed a white blood count of 8,800, a red blood count of

5,370,000, and a hemoglobin of 15 Gm. (97 per cent). The differential white blood count was normal. The Kahn reaction of the blood was negative. The urine was normal. Two months after the onset, the heterophile agglutination test showed a normal reaction.

The rash disappeared within five days, at which time the temperature became normal. The infection subsided without further incident, except that the patient complained of weakness and a slow pulse rate. Three weeks after the onset (December, 1944) an electrocardiographic examination revealed a 2:1 auriculoventricular block with sinus arrhythmia. Further inquiry into the patient's history at this time revealed no preceding illness. A report from a university health service revealed that in March, 1940, the patient's pulse rate was 78 per minute, and there were no abnormal heart findings. The roentgen examination of the chest was negative.

At weekly intervals, the patient was given quinidine, prostigmin and atropine, and the effects of these drugs upon the block were observed by electrocardiography.

After taking an electrocardiogram (Classical leads I, II, III, aVl, aVf, and aVr, and multiple chest leads CF<sub>1-6</sub> (Fig. 1A) the patient was given 0.8 Gm. of quinidine sulfate orally. Two hours later, another tracing was taken, (Fig. 1B) and it was noted that the chief effects consisted of an acceleration of the average rate from 72 to 88 per minute, with a slight increase in the amplitude of the P-waves.

One week later a similar study was conducted using 1 mg. of prostigmin methylsulfate (Neostigmin)\* intramuscularly. Subsequently, using

\*This material supplied by Hoffmann-La Roche Company.

\* From the Department of Medicine, The University of Chicago Medical School.

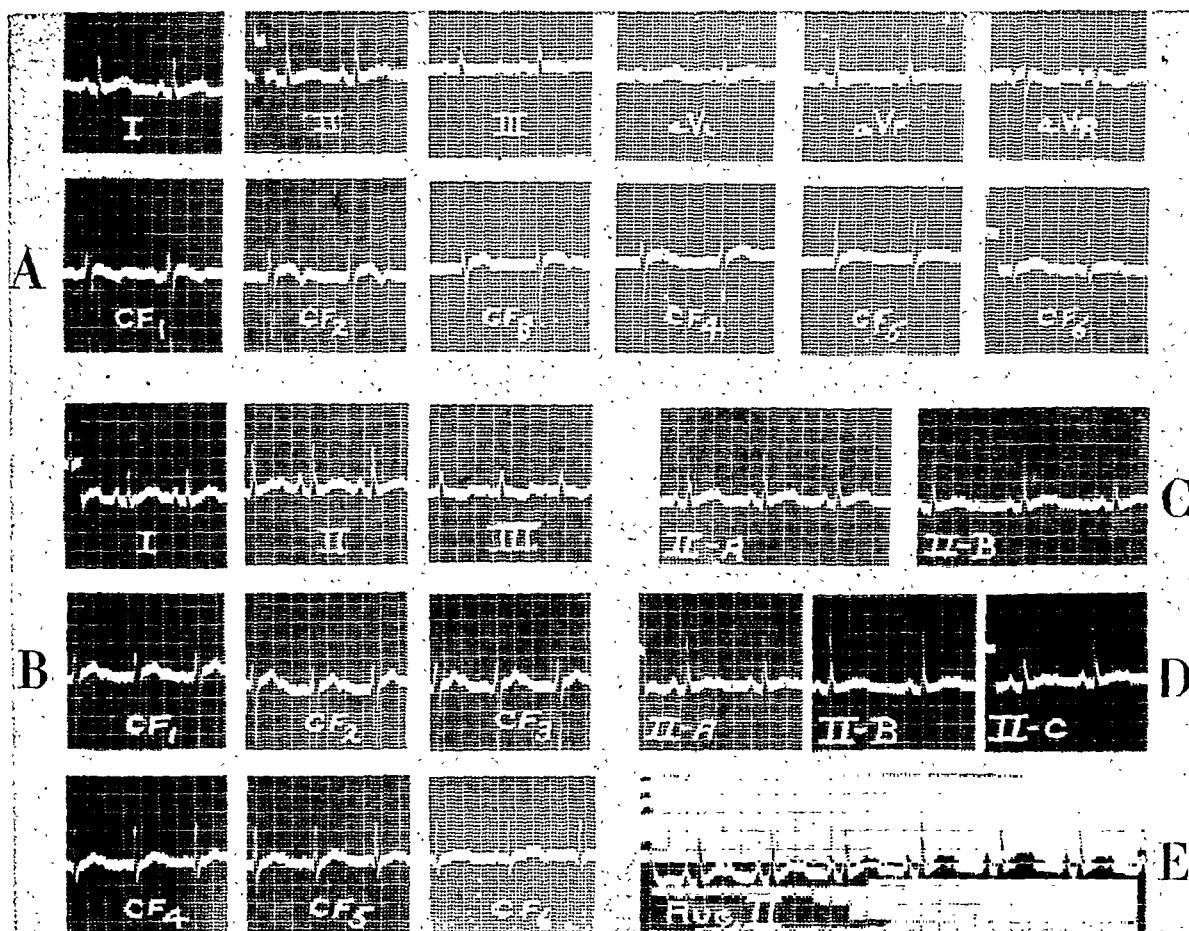


FIG. 1. A, Preliminary electrocardiographic study using classical leads I, II, III; unipolar extremity leads aVL, aVF, aVR; and multiple precordial leads CF<sub>1-6</sub>, which preceded the drug studies. Average rate of 72 per minute. B, two hours after oral dose of 0.8 Gm. of quinidine sulfate. Average rate of 88 per minute, using classical leads I, II, III, and CF<sub>1-6</sub>. C, II-A. Classical lead II preceding intramuscular injection of 1 mm. of prostigmin. Average rate of 73 per minute. II-B. Classical lead II, twenty-five minutes after injection of prostigmin. Average rate of 59 per minute. D, II-A. Classical lead II preceding subcutaneous injection of atropine sulfate 0.0013 Gm. Average rate of 79 per minute. II-B. Classical lead II taken fifteen minutes after the injection of atropine. Average rate of 61 per minute. II-C. Classical lead II taken forty minutes after the injection of atropine. Average rate of 78 per minute. E, aug. II. Classical lead II with augmented voltage demonstrating fusion of T and P waves.

classical lead II, tracings were taken at five-minute intervals for forty-five minutes. The average rate was slowed from 73 to 59 per minute with the maximum effect at 25 minutes after the injection, (Fig. 1c) which was in close accordance with previous findings.<sup>4</sup>

Atropine sulfate, 0.0013 Gm., was injected subcutaneously and again using classical lead II, tracings were obtained at five minute intervals for forty-five minutes. The average rate was slowed from 70 to 61 per minute within fifteen minutes after the injection, (Fig. 1d) and at forty

minutes after the injection, the average rate was accelerated to 78 per minute. (Fig. 1d.)

Subsequent electrocardiograms revealed that the block persisted in 2:1 rhythm with mild sinus arrhythmia. A tracing (Fig. 1e) using doubly augmented voltage demonstrated fusion of the T and P waves.

#### COMMENTS

Most of the textbooks of medicine, cardiology, electrocardiography and most of the reports in the literature in their discus-

sion of heart block do not mention measles or German measles as etiological factors, but they do mention other etiological factors such as rheumatic fever,<sup>5,6,7,8</sup> diphtheria,<sup>7,9</sup> congenital deformities of the septum,<sup>10</sup> uremia, asphyxia, syphilis, influenza,<sup>11,12</sup> scarlet fever, streptococcic infections, typhoid fever,<sup>13</sup> typhus fever, tonsillitis,<sup>14,15</sup> pneumonia,<sup>16</sup> excessive vagal stimulation,<sup>17</sup> coronary diseases,<sup>18</sup> secondary tumor growth<sup>19</sup> and various toxic agents.

The earliest comments concerning heart block due to measles were made at the turn of the century in 1903 by Burzi,<sup>1</sup> who described a case of complete auriculo-ventricular heart block with low pulse rates and Morgagni-Adams-Stokes seizures, occurring as an attack of measles was receding. The heart block was transient and the patient recovered fully.

Zahorsky,<sup>2</sup> in 1905, described a case of "cardiac asthenia" due to measles, but this article is not accessible, and it could not be determined whether this case did or did not have heart block.

Logue and Hanson<sup>3</sup> recently reported a case of temporary complete heart block due to German measles which occurred during the pre-eruptive stage. The administration of atropine sulfate decreased the degree of block from 3:2 rhythm to 1:1 rhythm.

Stein and Uhr,<sup>10</sup> in reporting a case of congenital heart block, did not consider it significant that the child had had German measles sixteen months prior to detection of the block, although on three earlier examinations no comment concerning abnormalities of the heart was recorded.

Eyster and Middleton,<sup>7</sup> reporting auriculoventricular heart block in children, mentioned one case wherein "measles and 'inflammation of the heart valves,' " preceded the examination.

White<sup>20</sup> does not consider atropine worthwhile in permanent 2:1 heart block, and it

was ineffective in the case we are reporting. (Fig. 1D.)

#### SUMMARY

1. A case of permanent 2:1 auriculo-ventricular heart block following German measles is reported.

2. A review of the literature revealed no similar case report, although reference was made to two cases of temporary heart block following measles.

3. The effects of the following drugs were noted through electrocardiography: (1) The average rate was accelerated from 72 to 88 per minute at two hours after the oral administration of 0.8 Gm. of quinidine sulfate. (2) The intramuscular injection of 1 mg. of prostigmin slowed the average rate twenty-five minutes later from 73 to 59 per minute. (3) Atropine sulfate 0.0013 Gm., injected subcutaneously, slowed the average rate within fifteen minutes from 70 to 61 per minute, and forty minutes after the injection the average rate accelerated to 78 per minute.

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## The Dangerous Carrier of Hemolytic Streptococci

**A**MONG the most important problems in the field of communicable disease is that of the mode of spread of streptococcal infection. Little information concerning the origin of sporadic cases or of epidemics has been available. It is known that the carrier rate of Group A hemolytic streptococci is high when an epidemic of scarlet fever or streptococcal sore throat is occurring, but a high carrier rate does not necessarily result in an epidemic. The real significance of the high carrier rate was brought out by Schwentker<sup>1</sup> in his study of scarlet fever at Fort Warren, Wyoming, where he found that the greatly increased incidence of Group A streptococcus carriers which occurred in those companies exhibiting a high morbidity of scarlet fever was due to the epidemic strain, Type 19. But what initiates such an epidemic, *i.e.*, what constitutes the conditions which give rise to the initial cases has, up to the present, not been understood.

An observation made by Gordon<sup>2</sup> a number of years ago gave a clue to the elucidation of this problem. He found that scarlet fever patients who had had a complicating sinusitis or rhinitis were much more prone to cause secondary cases of scarlet fever after leaving the hospital than were the usual run of convalescents from this disease. The significance of this observation was not appreciated, probably because of the undeveloped state of the subject at that time. It was not

until the recent war that further rapid progress in the understanding of the mechanism of transmission of streptococcal infection was made. The studies of Hamburger and associates, working under the Commission of Air-Borne Infections of the U. S. Army Epidemiological Board, clarified many little understood problems in this field and culminated in the discovery of the dangerous carrier of hemolytic streptococci.

The initial stimulus leading to their investigations was the finding that in certain hospital wards housing common respiratory disease the presence of Group A hemolytic streptococci in the throats of as many as 50 per cent of the patients resulted in no cases of streptococcal disease or of non-symptomatic infection of other patients, whereas in another ward a single carrier of one of these same types of streptococci might give rise to a number of cases of streptococcal infection. A second observation of importance was that when blood agar settling plates were put on each bedside table in a ward of scarlet fever convalescents, the number of hemolytic streptococci recovered from the air was consistently greater day after day beside one or two patients.<sup>3</sup> This led to an intensive study of the environment of such patients and it was found that their bedding, clothing and the floor dust about the bed were much more heavily contaminated with streptococci (of the type

<sup>1</sup> SCHWENTKER, F. The relation between scarlet fever morbidity and streptococcus carrier rates. *Am. J. Hyg.*, 38: 207-210, 1943.

<sup>2</sup> GORDON, J. E. Epidemiology of scarlet fever. A clinical approach. *J. A. M. A.*, 98: 519-523, 1932.

<sup>3</sup> HAMBURGER, M. JR., PUCK, T. T., HAMBURGER, V. G. and JOHNSON, M. A. Studies on the transmission of hemolytic streptococcus infections. III. Hemolytic streptococci in the air, floor dust, and bedclothing of hospital wards and their relation to cross infections. *J. Infect. Dis.*, 75: 79-94, 1944.

present in the throat) than were the environments of the other ward patients. It was then discovered that the individuals who produced such marked contamination of their surroundings were those carrying hemolytic streptococci in their noses.<sup>4</sup> Quantitative studies of the dispersal of streptococci by throat carriers on the one hand, and nasal carriers (who almost always had positive throats also) on the other, showed that the nasal carrier dispersed 80 to 100 times as many streptococci as did the individual carrying these micro-organisms in the throat but not in the nose. Nasal carriers of hemolytic streptococci were found most commonly among convalescents from streptococcal disease but a considerable number appeared quite well and gave no history of infection although an analysis of this latter group by means of antistreptolysin titers of the blood serum indicated that most of them represented missed cases.<sup>5</sup> Further studies showed that blowing the nose and sneezing produced the greatest dispersal of streptococci from the nasal carrier and that contamination of the hands, particularly from the nose-blow, constituted the principal means of conveying streptococci to the immediate environment.<sup>6</sup>

Direct evidence that such carriers were dangerous came from an epidemiological study of cross infections in hospital wards and cases occurring in barracks.<sup>7</sup> Nearly all

the hospital cross infections were traced to a single nasal carrier who exhibited a high "streptococcal output" while other carriers on the same ward putting out relatively small numbers of streptococci, with one exception, failed to spread infection. Similarly, outbreaks of streptococcal disease in barracks were traced to a single nasal carrier of the type causing the infection. This aspect of the study was amplified by Loosli, Lemon and co-workers,<sup>8</sup> also working under the Commission on Air-Borne Infections, to include the pattern of streptococcal contamination of the environment in relation to spread of disease among the occupants of the barrack. The most striking example of the menace presented by the nasal carrier dispersing large numbers of hemolytic streptococci came from the study of a food-borne epidemic of Type I streptococcal infection involving more than 100 convalescent patients who ate in the hospital mess.<sup>7</sup> The outbreak was traced to a "cold food handler" with strongly positive nose and throat cultures and tremendous contamination of the hands. The probable vectors were salad and pie which he sliced and wrapped separately "to keep each piece clean."

In an attempt to clear up the nasal carrier state, groups of such carriers were treated by Hamburger and Lemon<sup>9</sup> with sulfadiazine and penicillin. The most promising results came from the use of calcium penicillin in beeswax-peanut oil in a daily dosage of 300,000 units. Streptococci disappeared from the nose and throat shortly after beginning treatment and did not return in half the cases following cessation of the drug. Due to insufficient supply, it was not possible to continue treatment for more than five days.

<sup>4</sup> HAMBURGER, M. JR., GREEN, M. J. and HAMBURGER, V. G. The problem of the "dangerous carrier" of hemolytic streptococci. I. Number of hemolytic streptococci expelled by carriers with positive and negative nose cultures. *J. Infect. Dis.*, 77: 68-81, 1945.

<sup>5</sup> LEMON, H. M. and HAMBURGER, M. J. Missed cases and contact carriers among nasal carriers of beta hemolytic streptococci. *J. Immunol.*, 54: 189-196, 1946.

<sup>6</sup> HAMBURGER, M., JR., GREEN, M. J. The problem of the "dangerous carrier" of hemolytic streptococci. IV. Observations upon the role of the hands, of blowing the nose, of sneezing and of coughing in the dispersal of these microorganisms. *J. Infect. Dis.*, 79: 33-44, 1946.

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<sup>9</sup> HAMBURGER, M. JR., and LEMON, H. M. The problem of the "dangerous carrier" of hemolytic streptococci. III. The chemotherapeutic control of nasal carriers. *J. A. M. A.*, 130: 836-841, 1946.

These studies have contributed most important knowledge concerning the manner in which streptococcal disease is spread and point out the direction in which rational control may proceed. While it may not be wise at the present time to neglect the non-nasal throat carrier entirely, it seems quite evident that the nasal carrier of hemolytic streptococci provides the chief source of infection and that effective control of such

carriers would constitute a long step forward in reducing the incidence of this disease. This knowledge should also be most helpful in resolving the confusion of the present quarantine regulations which keep scarlet fever patients isolated for varying periods of two to three weeks and ignore cases of nasopharyngitis due to the same micro-organism.

O. H. ROBERTSON, M.D.

## Quantitative Aspects of Benzoyl Glucuronate Formation in Normal Individuals and in Patients with Liver Disorders<sup>\*</sup>

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**A**FTER oral ingestion of 6 Gm. of sodium benzoate normal subjects excrete at least 4.5 Gm. of hippuric acid within four hours, that is, at least 3.0 Gm. of benzoic acid conjugated with the equivalent amount of glycine (Quick's test).<sup>1</sup> After ingestion of sodium benzoate not only hippuric acid but also benzoyl glucuronate appears in the urine.<sup>2,3,4,5</sup> Quick, in 1926, isolated this compound in pure crystalline form.<sup>6</sup> In previous publications, the authors with the collaboration of E. Greenspan<sup>7,8</sup> have shown by a qualitative method that there was a difference in glucuronic acid conjugation after the administration of equivalent doses of sodium benzoate and of benzoic acid. After 5.8 Gm. of sodium benzoate by mouth the glucuronate reactions in the urine become strongly positive. This was to be expected because Wagreich, Abrams, and Harrow<sup>5</sup> had shown that about 5 per cent of the ingested benzoate (5-7 Gm. dose) appeared in the urine conjugated with glucuronic acid. Their observations were in accord with the previous studies of Neuberg, and of Quick, who obtained 7 to 12 per cent and 10 to 12 per cent, respectively, in the form of benzoyl glucuronate, but gave somewhat

larger doses of sodium benzoate (8-15 Gm.).<sup>3,4</sup> When, however, we administered 5 Gm. of benzoic acid to normal persons, the glucuronate reactions in the urine were usually negative.

We could further ascertain that the condition of the liver function has an important influence upon the excretion of glucuronates. In a series of patients with impaired liver function even the ingestion of 5 Gm. of benzoic acid resulted in the excretion of considerable amounts of glucuronates.

In this study it will be shown that the qualitative differences observed in the glucuronate excretion after ingestion of sodium benzoate and of benzoic acid can be substantiated by quantitative analyses.

The direct quantitative measurement of benzoyl glucuronate is not possible. The reducing power of the urine cannot be used for the determination of benzoyl glucuronate because it is well known that the urine normally contains reducing substances other than glucuronic acid. Quantitative methods for glucuronic acid have been devised recently, but for our purpose they cannot be used because the urine normally contains varying amounts of glucuronates.

The amount of benzoyl glucuronate can

<sup>\*</sup> From the Second Medical Service of the Mount Sinai Hospital, New York.

be calculated, however, by the difference between the total benzoic acid and hippuric acid values in the urine. This method first used by J. Neuberg<sup>3</sup> and later by Quick<sup>9</sup> gives satisfactory results because after ingestion of sodium benzoate or benzoic acid no appreciable quantities of free benzoic are excreted.

In order to increase the accuracy of the determinations a few minor modifications of the method were introduced.

#### METHOD

Breakfast is omitted, and either 5 Gm. of benzoic acid or 5.8 Gm. of sodium benzoate are ingested within ten minutes. Lunch is allowed, but fruits and fruit juices are withheld. Powder wafers can be used to avoid the unpleasant taste, but we found it more certain and agreeable to give the dose in gelatin capsules the latter having no delaying effect on absorption. Excessive drinking of water is discouraged.

Urine is collected at two, four and six hours after the administration of the drug. The entire sample is saved. The urine is kept in the icebox until used later in the day. If left longer, it should be rendered acid to litmus.

*Test for Glucuronic Acid.* A one-thousandth part of the urine volume of each specimen is measured into a test tube and diluted to 2 cc. with water. If, for instance, the specimen measures 230 cc., then 0.23 cc. is taken for analysis. Two cc. of concentrated HCl and finally 2 cc. of 0.2 per cent aqueous, fresh naphthoresorcinol solution are added and mixed. The test tubes are placed in a boiling water bath for exactly ten minutes, then cooled in running water. Two cc. of amyl alcohol (*iso*) are used to extract the blue color. The color should be read immediately with a fluorescent lamp behind the tube.

Occasionally a greenish-blue or brown color appears that causes uncertainty in the

reading of the test. To remove the interfering substances the lead precipitation method of Salt<sup>10</sup> is applied. One-thousandth of the urine volume is pipetted into each of four graduated 10 cc. centrifuge tubes, and diluted to 2 cc. with water. To the tubes respectively 0.05, 0.1, 0.15, and 0.2 cc. 5 per cent lead acetate are added, the contents mixed and centrifuged. Then one drop of lead acetate is added to each of the tubes and the tube selected in which precipitation is seen to be just complete. If no tube is completely precipitated, an additional 0.2 cc. of lead acetate is added to each and the procedure is repeated. Complete precipitation is thus effected but an appreciable excess of lead acetate is avoided. The supernatant fluid is poured from the selected tube into another centrifuge tube and N sodium hydroxide added dropwise until the first permanent precipitate of lead hydroxide is observed. Then 0.6 cc. of basic lead acetate (10 per cent) is added, the contents mixed and centrifuged. Now one drop more of the reagent is added. If this causes precipitation, an additional quantity of basic lead acetate is added. The process is repeated until a slight excess is present and precipitation is complete. The supernatant fluid is poured away and the deposit washed on the centrifuge by thoroughly stirring with 1 cc. water and separating.

The precipitate is transferred to a test tube using two 2 cc. portions of diluted HCl (1:1). Two cc. of 0.2 per cent naphthoresorcinol solution are added and mixed. The boiling and extraction of the blue color proceeds according to the method given above.

The three urine specimens are then thoroughly mixed and the volume measured. If the total volume is below 350 cc., water is added to that level. Two 20 cc. aliquots are taken for determination of total benzoic acid and similarly two 20 cc. specimens for determination of hippuric acid.

*Total benzoic acid* is determined by the

method of Kingsbury and Swanson<sup>11</sup> (using Neuberg's modification)<sup>3</sup> as follows:

The 20 cc. aliquots are placed into 300 cc. Kjeldahl flasks and diluted to 50 cc. Then 7.5 Gm. of sodium hydroxide, 0.5 Gm. of magnesium oxide and 2 glass beads are added, and the mixture gently boiled for one half hour on a hot plate. At the end of this time, while still at the boiling temperature, 1.0 cc. of a 7 per cent solution of potassium permanganate is added, care being taken to rinse down any permanganate that may remain in the neck of the flask with the smallest possible amount of water. The flask with its brown contents is twirled gently for a minute or two, cooled under the tap, and left at room temperature for at least two hours. Water jacketed condensers with rubber stoppers are placed on the necks, and 30 cc. concentrated nitric acid slowly poured down the side of each condenser (it is advisable to do this in a hood). The mixture is now gently boiled for forty-five minutes, cooled under the tap and the extraction with chloroform carried out.

The condenser is rinsed down with 25 cc. of water to remove any benzoic acid sublimated at the bottom of the condenser. The contents of the flask are transferred to a 500 cc. separatory funnel containing 25 Gm. of ammonium sulfate. The flask is rinsed with 20 cc. of water which is then added to the separatory funnel. After dissolving the ammonium sulfate the benzoic acid is extracted successively with one 50 cc., one 35 cc. and two 25 cc. portions of neutral, well washed chloroform. The first two portions of the chloroform are used to rinse the Kjeldahl flask. As each chloroform fraction is separated, it is poured through a folded filter paper into a second separatory funnel. The filter paper is washed with 10 cc. of chloroform.

The combined extracts in the second separatory funnel are washed once with 100 cc. of Folin-Flander's salt solution (con-

taining 1.0 cc. of concentrated HCl in 2 liters of saturated NaCl solution). The funnel tips are dried with absorbent filter paper in order to remove remnants of the Folin-Flander's solution and the chloroform layer drawn off through a dry filter paper into a dry Erlenmeyer flask. The watery phase remaining in the separatory funnel is shaken with 20 cc. of chloroform. Again the funnel tips are dried with strips of absorbent filter paper. The chloroform is drawn off into a small beaker to which the wet folded filter paper has been transferred, thereby rinsing the paper with the chloroform. The latter is then poured through a fresh filter paper into the main bulk of chloroform in the Erlenmeyer flask.

All extractions are performed by shaking for three minutes, and allowing one half hour periods for complete separation, (assisted by a few twirls). Four drops of 1 per cent phenolphthalein in absolute alcohol are added to the benzoic acid solution. Then the solution is titrated to a faint but definite pink with tenth-normal sodium ethylate (standardized against benzoic acid). Duplicates tally very closely.

*Hippuric Acid (Quick's Method).*<sup>9</sup> The aliquot of 20 cc. of urine is placed in a continuous ether extractor and acidified with 0.5 cc. of 5N sulfuric acid. The perforations of the inner extractor tube should be on a flat surface and face downwards. Ether is added, and the extractors placed in a sand bath heated by a medium sized hot plate. Water jacketed condensers are then placed in the mouths, using cork stoppers. The extraction proceeds at a rapid pace for exactly four hours, when the sand bath is removed and the extractors allowed to cool. The ether is distilled off using a water bath.

To the crystals in the 250 cc. Erlenmeyer flask, 25 cc. of concentrated HCl are added and mixed. Hydrolysis is accomplished by refluxing on the hot plate (low setting)

under an air condenser for two hours (in hood). The contents of the flask are transferred to an evaporating dish and dried completely on the water bath. The contents of the evaporating dish are then dissolved in hot water, filtered into 250 cc. beakers, washed with small quantities of water, and the filter paper washed in the dish with a further portion of hot water, filtering the latter through a fresh filter paper.

The glycine present is determined by a formol titration. The glycine containing solution obtained after hydrolysis is often colored which makes the use of indicators to determine the end points of the formol titration inadvisable. In order to avoid this difficulty we performed the titration with the help of an electrical pH indicator apparatus (Fisher titrimeter, new model). A potentiometric titration can be conveniently done with an accuracy better than 0.1 pH unit, if one uses ordinary care. The instrument is calibrated (after warm up) with a known buffer of pH 7.0 (glass and calomel electrodes, and the motor-driven glass stirrer are used). Then the glycine containing solution is neutralized to pH 7.0. Ten cc. of formaldehyde (neutralized to pH 7.0 just before use) are added, and titrated with 0.1 N NaOH to pH 8.9. Duplicates agree closely. The equivalence point of pH 8.9 was determined by formol titration of pure glycine and hydrolized hippuric acid solutions.

In order to determine the time necessary for complete extraction of hippuric acid from the urine, 300 mg. of hippuric acid were added to 20 cc. of normal urine. The hippuric acid obtained after extraction lasting for three hours, four hours and five hours was determined. With the continuous ether extractor used for these experiments, the optimal time of extraction appeared to be four hours.

COMMENTS

The results obtained are shown in Tables I, II and III. These figures indicate that the qualitative changes of the glucuronate reactions in the urine run parallel with the quantity of benzoic acid which is not conjugated with glycine.

TABLE I  
ADMINISTRATION OF 5.8 GM OF SODIUM BENZOATE  
TO NORMAL SUBJECTS

Name	Naphthoresorcinol*	A	B	A - B	Per Cent of A
		Total Benzoic Acid, Gm.	Glycine Bound Benzoic Acid, Gm.	Non-hippuric Benzoic Acid, Gm.	
1. SA	+++ — —	4.77	4.27	0.50	(10.6)
2. SN	+++ + —	4.96	4.65	0.31	(6.3)
3. SN	+++ +++ —	5.22	4.68	0.54	(10.3)
4. GA	+++ ++ —	4.66	4.47	0.19	(4.1)
5. LI	+++ +++ —	4.91	3.76	1.15	(23.4)
6. ER	++ +++ —	5.83	5.46	0.37	(6.3)

\* The plus and minus signs refer to the three 2-hour specimens collected.

After administration of 5.8 Gm. of sodium benzoate to normal persons, the glucuronate reactions in the urine are positive and the amount of benzoic acid not conjugated with glycine varies between 4.1 and 23.4 per cent. (Table I.)

After administration of 5 Gm. of benzoic acid to normal persons the glucuronate reactions in the urine are negative and the

amount of benzoic acid not conjugated with glycine varies between  $-3.1$  and  $+1.2$  per cent. (Table II.)

TABLE II  
ADMINISTRATION OF 5 GM. OF BENZOIC ACID TO NORMAL SUBJECTS

Name	Naph-thore-sorcinol*	A Total Benzoic Acid, Gm.	B Glycine Bound Benzoic Acid, Gm.	A - B Non-hippuric Benzoic Acid, Gm.	Per Cent of A
1. SA	— — —	4.85	4.79	0.06	(+1.2)
2. SN	— — —	5.52	5.57	-0.05	(-0.9)
3. GA	— — —	4.98	4.98	0.00	(0.0)
4. LI	— + —	5.15	5.14	0.01	(0.02)
5. ER	— — —	3.50	3.61	-0.11	(-3.1)
6. WA	— — —	3.82	3.85	-0.03	(-0.8)

\* The plus and minus signs refer to the three 2-hour specimens collected.

After administration of 5 Gm. of benzoic acid to patients with impaired liver function the glucuronate reactions in the urine are positive and the amount of benzoic acid not conjugated with glycine varies between 5.8 and 49.8 per cent. (Table III.)

These quantitative analyses bear out the conclusion that in patients with liver impairment, the administration of 5 Gm. of benzoic acid is followed by the excretion of considerable quantities of benzoyl glucuronate. This is in contrast to findings in normal persons in whom administration of

5 Gm. of benzoic acid does not give rise to the formation of benzoyl glucuronate.

For the explanation of this difference it should be pointed out that the rate of the

TABLE III  
ADMINISTRATION OF 5 GM. OF BENZOIC ACID TO PATIENTS WITH IMPAIRMENT OF LIVER FUNCTION

Name	Disorder	Naph-thore-sorcinol*	A Total Benzoic Acid, Gm.	B Glycine Bound Benzoic Acid, Gm.	A - B Non-hippuric Benzoic Acid, Gm.	Per Cent of A
1. Cad.	Hepatitis	— — ++	1.80	1.52	0.28	(15.5)
2. Cas.	Hepatitis	— + ++	4.19	3.71†	0.48	(11.5)
3. Hir.	Hepatitis (arsenic)	+++ — —	4.26	4.00†	0.26	(6.1)
4. Can.	Hepatitis	+++ +++ ++	3.74	1.88	1.86	(49.8)
5. Stu.	Portal Cirrhosis	+++ +++ —	3.24	2.57	0.67	(20.8)
6. Mar.	Cholangiolitic Cirrhosis	+++ +++ +++	2.29	1.97	0.32	(13.9)
7. Bla.	Hyperthyroid	+ +++ ++	3.96	3.73†	0.23	(5.8)
8. Hor.	Hyperthyroid	++ +++ +	2.43	2.25	0.18	(7.4)

\* The plus and minus signs refer to the three 2-hour specimens collected.

† Hippuric acid values within normal limits.

formation of hippuric acid is not only an index of the rapidity of glycine conjugation but at the same time of the intensity of glycine production. The liver does not store glycine but can produce it for purposes of conjugation as needed.<sup>12</sup> Quick has calculated that the body can produce from 0.55 to 0.7 Gm. of glycine per hour, the amount depending roughly upon the surface area of the body. Ingestion of the rapidly absorbed sodium benzoate results in a greater con-



centration of benzoate in the liver than ingestion of the slowly absorbed benzoic acid.<sup>7</sup> In the first case the amount of glycine which the body can form is not sufficient to transform all the benzoate to hippuric acid and, therefore, part of the benzoic acid is excreted as benzoyl glucuronate. Glucuronic acid can also easily be formed in the human organism at the rate of nearly a Gm. per hour.<sup>13</sup> The quantities of benzoate which reach the liver during the slower absorption of benzoic acid never exceed the quantities which can be taken care of by the glycine production of the body. As a result no conjugation of benzoic acid with glucuronic acid takes place. This explanation is confirmed by slow ingestion of sodium benzoate which was proved not to give rise to formation of benzoyl glucuronate.<sup>7</sup>

The formation of benzoyl glucuronate after administration of 5 Gm. of benzoic acid to patients with impaired liver function can be explained in the same way. Here, the glucuronic acid evidently supplements the glycine conjugation of the benzoate which is decreased due to impairment of liver function. Quick already noted that in one patient with a liver disease who had ingested 5.8 Gm. of sodium benzoate, 21 per cent of the excreted benzoic acid was bound to glucuronic acid.<sup>4</sup> Several months later when her clinical condition had shown great improvement, she no longer excreted glucuronic acid when the same quantity of benzoate was again given. Quick, however, did not follow up this remarkable finding but elaborated the hippuric acid excretion after ingestion of sodium benzoate into the well known liver function test.

The compensatory conjugation of benzoic acid with glucuronic acid can be made to yield valuable clinical data; even in patients with normal hippuric acid excretion an excessive excretion of glucuronates may indicate impaired liver function. (Table III.)

## SUMMARY

The amounts of total benzoic acid and benzoic acid conjugated with glycine have been determined after administration of 5 Gm. of benzoic acid to normal persons and to patients with impairment of liver function.

Under these conditions the qualitative glucuronate reactions in the urine are negative in normal persons and the amount of total benzoic acid is equal to the quantity of benzoic acid excreted in the form of hippuric acid.

Under the same conditions the qualitative glucuronate reactions in the urine are positive in patients with impaired liver function, and the amount of total benzoic acid exceeds the quantity of benzoic acid excreted in the form of hippuric acid by 5.8 to 49.8 per cent.

It follows that the ingestion of 5 Gm. of benzoic acid does not lead to the excretion of benzoyl glucuronate in normal persons. Under the same conditions patients with impairment of liver function excrete considerable quantities of benzoyl glucuronate.

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# Excretion of Benzoyl Glucuronate as a Test of Liver Function\*

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RECENTLY the authors have shown that the Tollens' naphthoresorcinol reaction for glucuronates may be used as a quick clinical test to reveal excessive excretion of benzoyl glucuronate.<sup>1,2,3</sup> In this report the clinical application of this method will be presented and several diagnostic problems will be discussed.

## METHOD

Fasting normal volunteers and patients ingested 5 Gm. of benzoic acid† in gelatin capsules. Breakfast‡ was omitted. Lunch was allowed, but fruits and fruit juices were forbidden. Urine was collected at two, four and six hours after the administration of the drug. As a rule the entire sample was saved, but the loss of a *small* part of a two-hour specimen should cause no great concern, since the test is qualitative. The urine was kept in the icebox until used later in the day. If retained longer it was rendered acid to litmus.

*Test for Glucuronic Acid.* A one-thousandth part of the urine volume of each two-hour specimen is measured into a test tube and diluted to 2 cc. with water. If, for instance, the specimen measures 230 cc., 0.23 cc. is taken for analysis. Two cc. of concentrated HCl and finally 2 cc. of 0.2 per cent fresh aqueous naphthoresorcinol

† All subjects ingested benzoic acid as the acid and not as sodium benzoate; the latter causes positive glucuronate reactions even in normal persons.

‡ Glucose infusions should be discontinued while the test is being carried out.

solution are added and mixed. The test tubes are placed in a boiling water bath for exactly ten minutes, then cooled in running water. Two cc. of iso-amyl alcohol are used to extract the blue color. The color should be read immediately with a fluorescent lamp behind the tube.

Occasionally a bluish-green color appears, causing uncertainty in the reading of the test. To remove the interfering substances the lead precipitation method of Salt<sup>4</sup> is applied.<sup>3</sup>

The blue color which indicates a positive reaction can be graded as one, two or three plus.

## OBSERVATIONS

In normal persons neither the fasting urine nor the urine excreted after ingestion of 5 Gm. of benzoic acid shows positive naphthoresorcinol reactions with the method described. However, while it is true that the majority of normal persons have reactions which do not produce a blue color, it should be noted that the presence of a slight bluish tint in the second two-hour specimen is still within normal limits. (Table 1.) When the qualitative glucuronic acid test after the administration of 5 Gm. of benzoic acid is positive, the presence of hepatocellular damage is highly probable.

Three types of glucuronate pattern have been observed according to the time elapsing before the appearance of a positive reaction. The degree of hepatocellular damage can

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be estimated grossly from the abnormal patterns, a delay in glucuronate conjugation signifying a more severe type of liver disturbance. However, as there are exceptions to this rule, the results are usually reported as normal or abnormal glucuronate pattern. (Table I.)

TABLE I  
TYPICAL GLUCURONATE PATTERNS OBTAINED AFTER  
INGESTION OF FIVE GM. OF BENZOIC ACID\*

Normal Patterns	Positive or Abnormal Patterns					
	Minimal Damage		Moderate Damage		Severe Damage	
2 hr. — —	—	—	+++	+++	—	—
4 hr. — +	++	+++	—	++	—	+
6 hr. — —	—	—	—	—	+++	++

\* The qualitative glucuronate test is positive when a blue color is produced by the naphthoresorcinol method described in the text. The intensity of the blue color can be graded as one, two or three plus.

Nausea and vomiting occurred rarely, being much less frequently observed than with the routine oral hippuric acid test.

#### COMMENTS

Table II contains the results obtained by application of the naphthoresorcinol test to the urine after ingestion of 5 Gm. of benzoic acid. Twenty-three normal subjects and one hundred patients free from apparent hepatic disturbances showed normal glucuronate patterns without exception. In eighty-nine patients who were under study because of possible disease of the liver, the glucuronate test proved to be a useful gauge of liver function.

All of the twenty-two patients with infectious jaundice and the two patients with toxic hepatitis (arsenic) showed abnormal glucuronate patterns. This test can easily be performed on admission to the hospital, and since the results are immediately available, it assists in early diagnosis. While in the vast majority of patients with hepatitis

an abnormal test was obtained on admission to the hospital, there was one exception in whom the glucuronate pattern was not immediately abnormal. When the test was re-

TABLE II  
BENZOYL GLUCURONATE EXCRETION AFTER 5 GM.  
BENZOIC ACID IN NORMAL SUBJECTS AND IN PATIENTS  
WITH AND WITHOUT HEPATIC DISORDERS

	Naphthoresorcinol Test		
	Ab- normal	Nor- mal	Totals
Normal subjects (volunteer physicians) . . . . .	0	23	23
Patients having no hepatic disturbance . . . . .	0	100	100
Hepatitis, catarrhal . . . . .	22	0	22
Hepatitis, toxic, arsenic* . . . . .	2	0	2
Cirrhosis, Laennec's . . . . .	23	0	23
Cirrhosis, cholangiolitic* . . . . .	1	0	1
Cirrhosis with hepatoma* . . . . .	1	0	1
Thyrotoxicosis* . . . . .	9	6	15
Liver metastases:			
From carcinoma of bronchus* . . . . .	2	0	2
From carcinoma of gallbladder* . . . . .	1	0	1
From unknown primary site* . . . . .	3	1	4
From body of pancreas* . . . . .	0	1	1
From sarcoma of uterus* . . . . .	1	0	1
Obstructive jaundice due to:			
Stone in common duct* . . . . .	0	2	2
Stricture of common duct* . . . . .	0	2	2
Metastasis occluding hepatic duct <sup>a</sup> . . . . .	0	1	1
Carcinoma of ampulla of Vater* . . . . .	0	1	1
Cholangiolitis and pericholangiolitis* . . . . .	0	1	1
Lymphomas <sup>b</sup> with liver involvement* . . . . .	0	9	9

\* Diagnosis confirmed by biopsy, operation, or autopsy.

<sup>a</sup> No metastasis to liver.

<sup>b</sup> Leukemia, hemoblastoma, lymphosarcoma, Hodgkin's disease, giant follicular lymphoblastoma.

peated it yielded unequivocal evidence of severe liver damage.

Twenty-five patients with cirrhosis of the liver were studied; abnormal glucuronate patterns were found in all.

Nine out of fifteen patients with thyrotoxicosis had abnormal glucuronate patterns. In these cases it was noted that the

color was almost always intensely blue. It is probable that in the hyperthyroid patients two factors are responsible for positive results: (1) Because of more rapid absorption, more benzoic acid reaches the liver per unit time, exceeding the normal rate of glycine production and conjugation so that free benzoic acid is left to be bound with glucuronic acid. (2) Excessive glycogenolysis causes hepatic dysfunction.

The first explanation is supported by the following experience. In contrast to the results obtained in normal persons, the hippuric acid excretion after ingestion of 5 Gm. of benzoic acid by hyperthyroid patients was in several instances largest in the first two-hour specimen. However, since in hyperthyroidism other liver function tests are also frequently indicative of hepatic dysfunction, in the final analysis both factors are probably contributory.

One subject, a "normal" volunteer (not included in Table II), repeatedly showed abnormal glucuronate patterns. Nevertheless the hippuric acid excretion after 5 Gm. of benzoic acid was normal, and the cephalin flocculation of the serum was only two plus. The naphthoresorcinol test in this subject was strongly positive in the two-hour and four-hour specimens, a finding suggestive of thyroid hyperactivity. On examination a marked tremor was elicited, the thyroid gland was just palpable, and the basal metabolic rate was reported as plus 22 per cent. In this case the abnormal glucuronate pattern revealed a mild hyperthyroidism which had not been detected previously.

There exists such a galaxy of liver function tests that the introduction of a new liver function test requires justification. It is not sufficient that the determination of the glucuronate pattern after ingestion of 5 Gm. of benzoic acid is a simple procedure, or that the test described is less complicated and entails fewer errors than the quantitative

determination of hippuric acid. A new reaction would be superfluous if the results merely confirmed the conclusions obtained by current liver function tests.

The following observations are reported to illustrate that although in many cases (I, II, V and VIII) the glucuronate tests run parallel with the other liver function tests, in doubtful cases (III, IV, VI and VII) the glucuronate pattern in combination with the other liver function tests may yield additional information.

CASE I. C. M., sixty-five years of age, a female, had had recurrent attacks of severe right upper quadrant pain for many years associated with intolerance to fatty food. Three weeks before admission the urine became dark, and the next day she noted jaundice which gradually increased in intensity. She lost only two pounds since the onset of jaundice. Stools were normal and there was no itching or chills.

On examination her temperature was normal; bradycardia was present. There was marked icterus of sclerae and skin. The liver was palpated two finger breadths below the costal margin and was tender, with a firm, smooth edge. The gallbladder was thought to be felt below the liver margin.

*Laboratory Data:\**

Urine—bile positive	
Urobilinogen present in dil. 1:5	
Stool brown, guaiac negative	
Erythrocyte sedimentation rate 2 mm./hr.	
Hemoglobin	80%
Prothrombin index	94%, 82%, 100%, 91%
Alk. phosphatase	32, 45, 13, 22 KA units
Thymol turbidity	4 plus, 4 plus, 4 plus
Cephalin flocculation test	4 plus, 4 plus, 4 plus, 3 plus, 3 plus
Hippuric acid	2.9 Gm. in 6 hours
Cholesterol/esters	360/150 280/130
Glucuronates 2 hr.	+++ -
4 hr.	+++ +
6 hr.	+++ ++
Icterus index	27, 12, 15
Bilirubin	3.2, 3.2 mg. %

\* When tests were repeated, several values are given.

Van den Bergh prompt positive

Albumin 3.7 Gm. %

Globulin 3.3 Gm. %

Total protein 7.0 Gm. %

X-ray examination failed to demonstrate the presence of radio-opaque biliary calculi, although the outline of the caudad portion of the fundus of the gallbladder was slightly denser than the remainder of the gallbladder. Oral cholecystography showed only very faint visualization of the gallbladder.

Because of the history of biliary colic and intolerance of fat, operative intervention was contemplated on admission. However, when all liver function tests pointed to widespread liver damage this was delayed. During five weeks of observation the icterus did not subside and the sedimentation rate rose to 58 mm./hr. Finally, because of an allegedly palpable gallbladder which appeared to increase in size, exploratory laparotomy was performed. Cirrhosis of the liver was found. Biopsy showed "severe acute and chronic portal inflammation with periportal fibrosis and moderate disorganization of liver architecture. The parenchyma was rich in bile pigment. Changes appeared to be those of cholangiolitic cirrhosis."

For many years this patient had been considered to be suffering from cholelithiasis. Although in the beginning the clinical picture seemed to indicate jaundice due to common duct stones, all the liver function tests including the glucuronate pattern indicated widespread liver damage.

CASE II. A. M., sixty-two years of age, a wine salesman, had lost 34 pounds in weight in the last year and a half. Although he drank much wine and other liquor, he also ate well. He had had intolerance to fatty foods for many years. Two months ago, after eating fried liver, he developed epigastric pain which lasted a few hours. At that time he also had a loose bowel movement, and his wife noted that he was yellow. The jaundice cleared after a few days.

Angiomas were found on both cheeks. The liver edge could be felt 3 cm. below the costal margin. Below the liver several observers could detect the presence of a large, firm gallbladder. A soft spleen was also just palpable.

#### *Laboratory Data:*

Urine bile 0 or 1 plus positive.

Urobilinogen present in dil. 1:30

Stool guaiac negative

Erythrocyte sedimentation rate 45 mm/hour

Prothrombin index 100%, 100%

Alkaline phosphatase 53 and 72 KA units

Thymol turbidity negative

Cephalin flocc. negative

Hippuric acid excretion 5.7 Gm. in 6 hr.

Icterus index 9

Bilirubin 1.1 mg. %

Cholesterol/esters 480/300

Galactose tolerance 0.5 Gm.

Glucuronate pattern normal

Exploratory laparotomy revealed the presence of amorphous stones in the common bile duct. The liver was normal.

In this slightly jaundiced patient who consumed large quantities of wine the diagnosis of cirrhosis seemed obvious. However, the glucuronate pattern together with the other liver tests all indicated the presence of obstruction of the common duct. At operation this was found.

CASE III. W. D., forty-seven years of age, a male, had a positive blood Wassermann in the early part of 1945 at the Red Cross Blood Bank. Although the patient was completely well and no abnormal signs could be elicited, anti-syphilitic treatment was started. The first injection of neo-arsphenamine was given August 25, 1945. The second injection on September 8, 1945, was followed by severe headache, nausea, vomiting, and fever of 102.5°F. Since then he had intermittent fever, anorexia, nausea, vomiting and dark urine. On September 19th, a third intravenous injection of neo-arsphenamine was followed after a few hours by high fever, chills, headache and malaise.

On admission the temperature was normal. Sclerae were icteric. The liver was one and one-half fingers down, smooth, and non-tender. The spleen could not be felt. The urine showed 2 plus albumin, 4 plus bile; hemoglobin 70 per cent, sedimentation rate 58 mm./hr., Wassermann positive.

Table III shows the results of the liver function tests. The currently used tests seemingly indicated that the patient had an obstructive type

of jaundice. In view of the history the diagnosis of cholangiolitic type of arsphenamine jaundice, as described by Hanger and Gutman, was in order.<sup>5</sup> However, the glucuronate pattern after ingestion of benzoic acid indicated that even this type of arsphenamine jaundice is associated with a considerable element of liver damage.

TABLE III  
COURSE OF PATIENT WITH OBSTRUCTIVE TYPE  
ARSPHENAMINE JAUNDICE (CASE III)

Date	Alkaline phosphatase	Icterus index	Bili-rubin mg. %	Van den Bergh	Ceph-alin flocc.	Glucuron-ate pattern
9/24	11 KA units	33	3.5	prompt pos. prompt pos. prompt pos. delayed negative	2 plus neg.	abnormal*
9/29	46 KA units	42	4.5			
10/1		18	2.6		1 plus neg.	abnormal†
10/3	29 KA units	12	1.2			
10/9	36 KA units	12	1.2			
10/14		7	1.0			
10/25	28 KA units					abnormal†

\* The usual benzoic acid test.  
† 5.8 Gm. sodium benzoate ingested in 9 portions over a 4 hour-period results in negative glucuronate reactions in normal individuals. Here the glucuronate reactions were positive.

This conclusion was helpful in the diagnosis of the following patient who actually had gallstones and in whom jaundice developed in the course of arsphenamine treatment.

CASE IV. J. H., a male, fifty-one years of age, had had two episodes of jaundice, one in 1917, the other in 1937. Six years before admission he suddenly felt severe epigastric pain which radiated to the back and up into the chest. A cholecystogram revealed the presence of gallstones.

In 1944, on the occasion of a routine checkup, signs of neurosyphilis were found, the Wassermann test being positive. He received bismuth injections at irregular intervals until February, 1946, when he was given weekly injections of neoarsphenamine. After four such injections he developed diarrhea, followed by nausea and chilly sensations. Within a week he became jaundiced, and the next day had pruritus, dark urine and clay colored stools. The jaundice remained essentially unchanged for the four weeks prior to admission, except that in the last week the stools became yellowish-brown.

On admission the temperature was normal. The pupils were irregular, did not react to light but reacted in accommodation. In the abdomen there was tenderness over the right upper quadrant. A firm liver edge was felt

3 finger breadths below the costal margin. The spleen could not be palpated.

The urine showed 4 plus bile. Urobilinogen was positive in a dilution of 1:5; erythrocyte sedimentation rate 70 mm/hr; hemoglobin 70 per cent, blood Wassermann positive.

While in the hospital the patient again experienced a severe attack of epigastric pain radiating to the back. Tenderness was elicited in the right upper quadrant of the abdomen.

TABLE IV  
LABORATORY FINDINGS IN EARLY-TYPE POST-  
ARSPHENAMINE JAUNDICE

	Case III	Case IV
Prothrombin time . . . . . (Index)	100 %	100 %
Alkaline phosphatase . . . .	46 KA units	35 KA units
Icterus index . . . . .	42	33
Cholesterol/esters . . . . .	760/245	600/300
Cephalin flocculation . . . .	2 +, neg., 1 +, neg.	2 +, neg.
Galactose tolerance . . . . .		1.9 Gm.
Thymol turbidity . . . . .		1 +, neg.
Hippuric acid* . . . . .	5.07 Gm. in 6 hr.	5.88 Gm. in 6 hr.
Glucuronate pattern after benzoic acid 5 grams . . .	2 hr. ++ 4 hr. +++ 6 hr. ++	2 hr. +++ 4 hr. - 6 hr. -

\* 5.0 Gm. in six hours is normal.

The chemical investigations (Table IV) showed a normal prothrombin time, increase of the alkaline phosphatase of the serum, normal cephalin flocculation and thymol turbidity tests, and normal galactose tolerance. After ingestion of 5 Gm. of benzoic acid the hippuric acid excretion was normal. All these tests did not make it possible to differentiate between jaundice due to gallstones and early-type post-arsphenamine jaundice. However, the strongly positive glucuronate excretion\* after ingestion of 5 Gm. of benzoic acid was sufficient to exclude common duct stone; this amount of liver damage indicated a post-arsphenamine hepatitis.

The clinicians and surgeons continued to feel uncomfortable about the diagnosis. One day they thought that a small tense gallbladder

\* Quantitative determination: 5.9 per cent of excreted benzoic acid was conjugated with glucuronic acid.<sup>3</sup>

could be palpated, and as a consequence, exploration could not be held off any longer. The gallbladder contained stones but the common duct was completely free. Cholecystectomy was performed. Liver biopsy showed typical findings of chronic inflammation of the periportal fields and capillary bile thrombi. The diagnosis of early-type post-arsphenamine hepatitis as indicated by the glucuronate pattern had been correct. In this patient the glucuronate pattern was the only test which indicated the correct diagnosis.

CASE V. P. R., a female, fifty-one years of age, had been suffering from gallstones for several years. These stones had been visualized radiographically. In addition, she also had anginal pains. There had probably been at least one episode of coronary thrombosis. During an examination in March, 1946, for new signs of coronary sclerosis, palpation of the abdomen was negative. In August, 1946, she consulted her physician because of the onset of epigastric pain and jaundice. In the two weeks prior to admission the jaundice was observed to be progressive.

On examination the liver was enlarged to one and one-half hand-breadths below the costal margin; the consistency was stony hard.

Laboratory methods showed absence of stercobilin in the stool, elevated serum bilirubin, direct Van den Bergh reaction, cephalin flocculation negative, hippuric acid excretion normal, alkaline phosphatase 28 KA units. The glucuronate pattern was normal. Therefore, the liver tests all indicated obstruction of the bile ducts with no hepatic impairment.

Exploratory laparotomy revealed carcinoma of the gallbladder with metastatic obstruction of the hepatic duct. There were metastases in the posterior abdominal wall, and in the suprapancreatic lymph nodes. The gallbladder contained numerous stones. The liver appeared free of metastasis.

In this patient the glucuronate pattern ran parallel with the other function tests. The obstructive jaundice was caused by metastases which had not as yet involved the liver parenchyma.

CASE VI. R. P., a female, fifty-two years of age entered the hospital because of constant

pain in the abdomen, mainly in the right upper quadrant, of eight weeks' duration. Associated with these symptoms was darkening of the urine and intermittent jaundice. Some relief was obtained by the application of hot compresses to the abdomen. Generalized pruritus and nausea were also present. She had lost 15 pounds in the past six weeks. This woman had intermittent gallbladder attacks for the past twenty years, but she never had jaundice and the liver had not been palpable.

On examination there was tenderness in the right upper quadrant with punch tenderness localized to the ninth costochondral junction. The liver was enlarged, the lower border being five finger breadths below the costal margin. The area of the gallbladder had a stony hard consistency; the spleen was also palpable.

#### *Laboratory Data:*

Urine—bile present  
Urobilinogen positive in dil. 1:100  
Sedimentation rate 58 mm/hr.  
Prothrombin index 84%  
Alk. phosphatase 28 Bodansky units  
Cholesterol/esters 600/300  
Cephalin flocculation negative  
Hippuric acid 4.5 Gm. in 6 hr.  
Glucuronate pattern abnormal 2 hr. +  
4 hr. —  
6 hr. —

Exploratory laparotomy was carried out and carcinoma of the gallbladder, with direct extension to liver and gastrohepatic ligament was found; a metastatic nodule was also found to obstruct the common duct. The liver, which was enlarged, contained many whitish metastatic nodules.

Although the current liver tests pointed to an extrahepatic obstructive jaundice, the abnormal glucuronate pattern indicated that in addition a general involvement of the liver parenchyma existed. This result was explained by the widespread metastases found at operation.

CASE VII. D. C., a female, fifty-five years of age, was admitted a second time because of progressive weakness, fatigue, exertional dyspnea and fever. Six months previously she had entered the hospital for unexplained fever and



prostration. Examination at that time revealed hepatosplenomegaly and a slightly enlarged heart. A few small axillary lymph nodes were also found. Biopsy showed the presence of a malignant reticulum cell proliferation. Transfusions and radiotherapy were of temporary benefit.

On examination numerous, firm, matted lymph nodes were found in the axillae, cervical and inguinal regions. The liver edge was palpable 2 cm. below the right costal margin, was firm and slightly tender. The spleen filled the entire left side of the abdomen. It was firm, tender and slightly irregular.

*Laboratory Data:*

Urine—albumin, trace

Blood Count:

Hemoglobin 42%

R.B.C. 2,800,000

W.B.C. 4,100

Differential: Monocytosis 14%

Bilirubin 0.2 mg. %

Bromsulfalein excretion normal

Hippuric acid excretion 4.1 Gm. in 6 hr.

Glucuronate pattern negative

Despite many transfusions and radiotherapy the course was gradually downhill, with terminal development of ascites and pleural effusion. Postmortem examination revealed hemoblastosis\* involving lymph nodes, liver and spleen.

We have obtained negative glucuronate patterns in patients with lymphomas† having liver involvement. This may prove useful in deciding against the diagnosis of hepatic cirrhosis.

CASE VIII. B. P., a female, forty-nine years of age, had a thyroidectomy for thyrotoxicosis sixteen years before admission. She was well until eight years before admission when intractable itching and patches of xanthelasma appeared on the eyelids. Jaundice was noted six years before the present admission, at which

\* Hemoblastosis is defined as a morbid process affecting the hematopoietic system with features of invasive growth as well as hyperplasia of spleen and liver, as in leukemia, but without any abnormality of the blood picture.

† See Table II.

time cholelithiasis was diagnosed. At operation gallstones were found, and a cholecystectomy performed. After the operation the jaundice persisted and the generalized pruritus became worse. While most of the stools were brown, on several occasions they were clay colored. Six weeks ago patient began to have diarrhea six to ten times daily, which persisted.

The skin was icteric and excoriated. An enlarged liver, rather tender, could be palpated with its border at the level of the umbilicus. The spleen was not enlarged.

*Laboratory Data:*

Urine—bile 4 plus

Urobilinogen positive in dil. 1:40

Stercobilin was present in the stool

Erythrocyte sedimentation rate 94 mm/hr.

Hemoglobin 88%

Galactose tolerance normal

Hippuric acid 2.6 Gm. in 6 hr.

Icterus index 30

Alk. phosphatase 25 KA units

Cephalin flocculation 1 plus

Prothrombin index 88%

Total protein 6.7 Gm. %

Cholesterol/esters 360/280

Glucuronate pattern normal

The jaundice was believed to be due to chronic obstruction of the common bile duct, caused either by stone or by a scar forming after the first operation. This diagnosis seemed justified in view of the almost normal cephalin flocculation test and the cholesterol ester ratio. On the other hand the alkaline phosphatase of the serum was not as much increased as expected in a case of obstructive jaundice of long standing, and the hippuric acid excretion was low. The glucuronate excretion being negative excluded generalized liver damage.

At operation the surgeons were convinced that cirrhosis of the liver was present. A tremendously enlarged liver, with a slightly nodular surface, and a greatly dilated hepatic artery and portal vein were found. The common bile duct could not be dissected as it was buried beneath dense adhesions. Liver biopsy, however, showed that the preoperative diagnosis had been correct. The specimen "consisted of a fragment of liver showing evidence

of chronic bile stasis (considerable number of bile thrombi, and bile pigment in Kupffer cells) and lymphocytic cells in periportal areas; general picture as found in obstructive icterus. Since normal architecture of liver lobules was not altered, cirrhosis can be ruled out."

From this case it may be concluded that although the glucuronate pattern is a relatively sensitive indicator of liver damage, it still remained negative in a patient with obstructive jaundice of very long standing.

#### SUMMARY

1. A simple liver function test is described which is based on the presence of excessive excretion of benzoyl glucuronate in the urine after ingestion of 5 Gm. of benzoic acid. The test is non-toxic and can be performed quickly. In selected cases, when used in conjunction with the current liver tests, it has important diagnostic application.

2. The test was studied in twenty-three normal volunteers, in a control series of 100 patients who had no obvious hepatic disturbances, and in eighty-nine other patients in whom hepatic disturbances were suspected.

3. In all normal volunteers, and in patients without hepatic disturbances the test was negative.

4. In all cases of hepatitis and portal cirrhosis the test was positive.

5. The test was also positive in some patients with thyrotoxicosis and in most cases of hepatic metastasis. It was negative in all of nine lymphomas.

6. Application to two cases of early-type post-arsphenamine jaundice is described. In both cases hepatocellular damage was indicated by positive tests. In one the diagnosis of arsphenamine hepatitis was made in the presence of gallstones.

7. The glucuronate reactions remained negative in a patient with obstructive jaundice of very long standing.

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# A Note on Studies of Hemolysis in Paroxysmal (Cold) Hemoglobinuria\*

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THIS is a brief preliminary note on studies relative to the mechanism of hemolysis in paroxysmal (cold) hemoglobinuria. The observations were made while studying a syphilitic negro male complaining of abdominal pain and dark urine after exposure to cold. The Donath-Landsteiner reaction<sup>1</sup> as done by a routine technic<sup>2</sup> was positive. Since there have been repeated clinical and experimental observations suggesting that some factor or factors other than cold may play an important rôle in the hemolytic mechanism of the disease,<sup>3,4,5</sup> the following work was done. The experiments are divided into three groups: (1) The first confirms Hijmans van den Bergh's observation<sup>4</sup> that CO<sub>2</sub>, under specified *in vitro* conditions, may effect the hemolysis of this disease; (2) the second indicates carbonic anhydrase inhibitors may, under certain circumstances, prevent the hemolysis; (3) the third shows that definite morphological changes of the erythrocytes occur prior to hemolysis.

## PROCEDURES

Group O erythrocytes were washed four times and resuspended in normal saline in 5 per cent concentration. Fresh guinea pig serum diluted 1:5 with normal saline was employed as complement. Serum was obtained from blood drawn from the patient and from normal subjects into warmed syringes and tubes. These components were proportioned as shown in Charts 1 and 2.

All tests were run in duplicate. The quantitative technics employed for CO<sub>2</sub>, cyanide and sulfanilamide determinations have been described elsewhere.<sup>6,7,8</sup> Hydrogen ion determinations were made with a Beckman meter at 27°C. The meter was calibrated repeatedly with a standard reference solution.

*Experiment No. 1.* CO<sub>2</sub>, helium and oxygen were collected in rubber bags and bubbled through pipettes into the combinations under oil for five minutes, as shown in Chart 1. The gases were collected in rubber bags and allowed to stand at the desired temperature before using, in order to avoid the cooling effects of a rapidly expanding gas. Additional controls were also set up under oil but did not receive any gas. As shown in Chart 1, hemolysis occurred only with CO<sub>2</sub> at 27°C. The pH of such a combination was 6.4 (8 volumes per cent CO<sub>2</sub>) and that of the combinations receiving oxygen or helium was 7.5 to 7.6. However, other observations suggest that the effect of CO<sub>2</sub> may not be due simply to a lowering of the pH, as it seems to be in nocturnal hemoglobinuria.<sup>9</sup> The pH of identical combinations was lowered to 6.2 by using saline acidified with HCl. Hemolysis did not occur. Nor did bubbling nitrogen into such acidified combinations under oil cause hemolysis, thus suggesting the CO<sub>2</sub> effect may not have been the summated result of lowered pH and trauma. Furthermore, a routine Ham test<sup>9</sup> was negative. The entire

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C H A R T 1										
TEST TUBE	PT. SERUM (cc)	CONT. SERUM (cc)	COMPL. (cc)	NORM. SALINE (cc)	CONT. R. B. C. (cc)	C O <sub>2</sub>	H <sub>E</sub>	O <sub>2</sub>	HEMOLYSIS AT 27°C	HEMOLYSIS AT 37°C
1	0.5		0.2	0.1	0.2	5 MINS			++++	0
2		0.5	0.2	0.1	0.2	5 MINS			0	0
3	0.5		0.2	0.1	0.2		5 MINS		0	0
4		0.5	0.2	0.1	0.2		5 MINS		0	0
5	0.5		0.2	0.1	0.2			5 MINS	0	0
6		0.5	0.2	0.1	0.2			5 MINS	0	0

CHART 1. Shows the degrees of hemolysis following the addition of carbon dioxide, helium or oxygen to various combinations at 27°C. and 37°C. Complete hemolysis is indicated by + + + +.

procedure was repeated at 37°C. after all the materials had stood at 37°C. for an hour. (Chart 1.) CO<sub>2</sub> did not cause hemolysis at that temperature. The serum hemolysin was then adsorbed on erythrocytes at 2°C. No hemolysis resulted from bubbling CO<sub>2</sub> at 25°C. into combinations similar to those of Chart 1 but made with serum from which the hemolysin had been adsorbed. Combinations containing the hemolysin and as low as 2.6 volumes per cent of CO<sub>2</sub> hemolyzed readily on chilling and warming.

*Experiment No. 2.* Cyanide and sulfanilamide inhibit the activity of carbonic anhydrase but sulfathiazole and sulfadiazine do not.<sup>10</sup> After several preliminary experiments the sodium salts of sulfanilamide, sulfadiazine, sulfathiazole and cyanide were employed in 0.008, 0.006, and 0.005 M. concentrations as shown in Chart 2. The pH of such combinations were 7.6 to 7.5 (27°C.). These tubes were chilled at 2°C. for ten minutes, then incubated at 37°C. for two hours. Hemolysis at the end of that time was absent or present only in traces

in the presence of cyanide and sulfanilamide; but hemolysis in those tubes containing equal amounts of sulfathiazole and sulfadiazine was practically complete. That cyanide and sulfanilamide did not destroy the hemolysin was demonstrated by the following experiment. Sulfanilamide and cyanide were added to two aliquots of serum in even higher concentrations (0.1 M.). The solutions were allowed to stand for three hours and then dialysed through cellophane bags suspended in normal saline for twenty-four hours. At the end of that time there was no detectable sulfanilamide and no more than a trace of cyanide in the sera. Both samples of serum retained their hemolytic activity as shown by Donath-Landsteiner tests, indicating the persistence of an active hemolysin. That these salts did not destroy the serum complement was shown by the hemolytic effect of such dialysed serum on sensitized sheep erythrocytes. The inhibition of hemolysis by sulfanilamide and cyanide, therefore, did not

C H A R T 2											
TEST TUBE	P.T. SERUM (cc)	COMPL. (cc)	CONT. R.B.C (cc)	SODIUM CYANIDE (cc)	SODIUM SULFA- NILAMIDE (cc)	SODIUM SULFA- THIAZOLE (cc)	SODIUM SULFA- DIAZINE (cc)	pH			HEMOLYSIS
								.008 M.	.006 M.	.005 M.	
CHILL	1	0.5	0.2	0.2	0.1			7.6			0
	2	0.5	0.2	0.2	0.1			7.5			0
	3	0.5	0.2	0.2	0.1				7.5		TRACE
AT	4	0.5	0.2	0.2		0.1		7.6			0
2° C	5	0.5	0.2	0.2		0.1		7.6			SL. TRACE
	6	0.5	0.2	0.2		0.1			7.6		TRACE
AND	7	0.5	0.2	0.2			0.1	7.6		+++	
WARM	8	0.5	0.2	0.2			0.1	7.5			+++
	9	0.5	0.2	0.2			0.1		7.5		+++
AT	10	0.5	0.2	0.2				0.1	7.6		+++
37° C	11	0.5	0.2	0.2				0.1	7.6		+++
	12	0.5	0.2	0.2				0.1		7.5	+++

CHART 2. Shows the degrees of hemolysis of various combinations following chilling for ten minutes at 2°c. and incubating for two hours at 37°c. Complete or almost complete hemolysis is indicated by +++.

result from destruction of the hemolysin or complement. It was a reversible inhibition.

*Experiment No. 3.* Suspensions of washed Group O erythrocytes in the patients' and controls' sera were studied microscopically. To the control sera was added enough lecithin to produce spherocytosis but not hemolysis. As has been shown, spherocytosis so produced causes no demonstrable alteration in cell volume.<sup>11</sup> First such suspensions were chilled to 2°c. for ten minutes, then placed in chilled hemocytometers and studied microscopically. Several hundred measurements of diameters of the cells in the control sera were made with a calibrated ocular-micrometer. No measurements were made on control suspensions after they had stood in the hemocytometer for more than four minutes in order to avoid evaporation with increased tonicity of the solutions. From such values the mean corpuscular volume (MCV) was calculated and checked by routine hematocrit and red blood cell counting methods.<sup>2</sup> Similar ocular-micrometer measurements were then made on the same control erythrocytes

chilled in the patient's serum and the MCV recalculated. While at very low temperatures the erythrocytes suspended in the patient's serum showed no or only occasional spherocytosis. Biconcave cells were prominent. However, as the hemocytometer warmed to room temperature the cells assumed a spherical appearance and gradually faded from view. Calculations ( $V = 4\pi r^3/3$ ) made from measurements of diameters of these spherocytes indicated no marked increase in cell volume. However, within a few seconds prior to the leakage and escape of hemoglobin the diameter of many of the lysing cells increased appreciably. Whether this was a result of an actual terminal increase in volume or simply a result of collapse of stroma associated with a loss of hemoglobin remains to be studied.

CASE REPORT

W. B. (J. H. H. history number 359265) was a 33 year old negro male who entered Johns Hopkins Hospital on December 5, 1945, with the complaints of abdominal pain and passage of dark urine following exposure to cold. The family history was non-contributory. The past

history revealed the patient had always enjoyed general good health until the present illness. In 1930, the patient had a penile sore and was given "needle treatment" by another clinic.

The present illness was dated by the patient as beginning three years prior to admission. He noticed short periodic attacks of nausea, cramping abdominal pain and vomiting associated with the passage of dark urine. These attacks occurred from a few minutes to several hours following chilling and exposure to cold. Between such episodes the patient was asymptomatic. During the summer months the attacks did not occur. The patient stated the abdominal pain would last only an hour or so and then disappear. This would be followed soon by the passage of dark urine. The urine would clear in a few hours and the patient would remain asymptomatic until subsequent exposure to cold. Exercise did not seem to precipitate an attack. The last episode of such symptoms had occurred a few days prior to admission following prolonged exposure to chilling of the feet during a hunting trip.

The physical examination revealed a temperature of 98.6°F.; pulse 64; respiration 20; and blood pressure 166/85. The patient was a well developed, well nourished colored male in no discomfort. The skin was moist. There were no eruptions. The pupils were round, regular and equal and reacted to light and accommodation. The retinæ showed no lesions. The extra-ocular movements were well performed. The external auditory canals were clear. Hearing was intact. The nasal septum was in the midline and not perforated. The nares were clear. The mucous membranes were of good color. The tongue protruded in the midline without tremor. There was no papillary atrophy. There was no pharyngeal or tonsillar injection. The neck was supple. The trachea was in the midline and the thyroid was not enlarged. There was no unusual cervical pulsation. Precordial dullness was not increased extending only to the mid-clavicular line in the left fifth interspace. There were no shocks, thrills or any unusual precordial activity. Heart sounds were of good quality. There was a soft systolic murmur at the apex that was not transmitted. Abdominal

examination revealed no masses or tenderness. No abdominal organs were palpable. The genitalia showed no scars. Neurological examination revealed no abnormalities.

**Laboratory Data:** The serological tests for syphilis were positive. Erythrocyte count was 4.31 million per cubic milliliter, hemoglobin was 11.8 Gm. per cent. Hematocrit was 35.7 per cent. The mean corpuscular volume was 83 cubic microns and the mean corpuscular hemoglobin concentration 32 per cent. Leukocyte count was 8,300. The sedimentation rate corrected to 1. The differential count showed 67 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 13 per cent lymphocytes, 19 per cent monocytes. The Ehrlich and Donath-Landsteiner tests were positive. Urine was dark with a specific gravity of 1.005, alkaline reaction and contained 2 plus albumin. There were no reducing substances. Microscopic examination showed 5 to 10 leukocytes per high power field but no casts or erythrocytes. Non-protein nitrogen was 123 mg. per cent. Phenolsulphonphthalein excretion was 38 per cent at the end of two hours. Serum bilirubin was 0.8 mg. per cent. The total serum protein was 7.06 Gm. per cent with albumin 4.19 and globulin; 2.87 urea clearance showed 48 per cent at the normal maximum. Cerebrospinal fluid showed a positive serological test for syphilis, 17 mg. per cent of protein, a negative mastic curve and 8 lymphocytes per cubic milliliter.

Stool examination was negative; X-rays of the chest and abdomen were interpreted as showing no abnormalities. On December 11, 1946, the non-protein nitrogen was 55 mg. per cent. *Diagnosis:* Syphilis, late, latent. Paroxysmal (cold) hemoglobinuria associated with impairment of renal function. In a period of thirteen days the patient was given 4,000,000 units of penicillin intramuscularly. He is now being followed in the Johns Hopkins Hospital Dispensary.

#### CONCLUSION

Under certain specified circumstances the addition of CO<sub>2</sub> to the serum from a patient with paroxysmal (cold) hemoglobinuria causes hemolysis. This effect of CO<sub>2</sub>

depends on the presence of a serum hemolysin. Evidence suggests it may not be due simply to a lowering of pH and occurs at temperatures which alone do not cause hemolysis. Sulfanilamide and cyanide, two substances which inhibit the activity of carbonic anhydrase, block the effect of this hemolysin in concentrations that do not destroy either the hemolysin or the complement. Their inhibitory effect is reversible. Preceding hemolysis the erythrocytes undergo marked morphological changes.

The authors wish to thank Drs. John Eager Howard, Harry Eagle and Merkel H. Jacobs for their ideas and comments.

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## Bacillus Pyocyaneus Infections<sup>\*</sup>

### *A Review, Report of Cases and Discussion of Newer Therapy Including Streptomycin (Concluded)*

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#### INTRACRANIAL INFECTIONS

*A. Pyocyaneus Meningitis.* Meningitis may occur as an extension from a neighboring focus in the sinuses or mastoids and as a localized infection of the meninges without systemic involvement especially following introduction of the organism during lumbar puncture or through cranial-cerebral trauma. It is a much more frequent complication of pyocyaneus sepsis than is endocarditis. The first proved case of meningitis due to this organism was reported in 1893 by Kossel.<sup>59</sup> Florence Evans<sup>58</sup> reviewed the literature on this subject in 1936, at which time she was able to find a total of forty cases (including two cases of Ehlers,<sup>57</sup> neither proved, and two cases ascribed to Charrin,<sup>56</sup> but which were those of Ehlers); eighteen of these were primary meningitis without generalized infection. She added three new cases of primary meningitis, all of which followed lumbar puncture. Since this time a number of other cases have been described.<sup>88-101</sup>

The report of Botterell and Magner<sup>101</sup> (1945) merits special consideration. Eleven cases of meningitis associated with penetrating head injuries were seen in patients evacuated from France during the Normandy campaign. They were all severe injuries. Nine patients died; two recovered.

<sup>\*</sup>From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

There were four cases of brain abscess; it seemed likely that *B. pyocyaneus* was present in three of these cases on admission. On admission in one other case the organism was cultured from the temporal muscle which was in communication with the subarachnoid space. In four cases the source seemed to be cross-infection (three from leaving a tube in the wound for repeated instillation of penicillin). Bacteriologic check showed that *B. pyocyaneus* was air-borne in some of the wards, all of which were crowded. In two cases it was thought that the meningeal infection resulted from intrathecal injection of contaminated penicillin. Although bacteriological check showed that the dispensed penicillin was sterile, the dregs of some of the bottles contained *B. pyocyaneus*. Infections with gram-positive organisms were well controlled with penicillin.

In Chart A the forty-one cases of primary *B. pyocyaneus* meningitis reported to this time are summarized. Thirty-two (78 per cent) of the total were the direct result of lumbar puncture and/or the introduction of contaminated solutions into the spinal or cranial subarachnoid space. Treatment has consisted in repeated spinal drainages and, recently, the use of sulfonamide compounds parenterally, orally



CHART A

SUMMARY OF CASES OF PRIMARY B. PYOCYANEUS MENINGITIS REPORTED IN THE LITERATURE

Author	No. of Cases	Origin	Outcome
Schlagenhauser <sup>67</sup> (1911) . . . . .	5	Infections followed spinal anesthesia (contaminated saline solution)	3 died 2 recovered
Chauffard and Laroche <sup>70</sup> (1917) . . . . .	1	Intraspinal administration of contaminated tetanus antitoxin	Recovery
Abadie and Laroche <sup>71</sup> (1918) . . . . .	1	Craniocerebral trauma (laceration of dura by shell fragments)	Recovery
Sonnenschein <sup>75</sup> (1923) . . . . .	1	Lumbar puncture	Death in 11 days
Schneider <sup>77</sup> (1924) . . . . .	1	Spinal anesthesia	Recovery in 3 months; (B. pyocyaneus in blood after onset of meningitis)
Levy and Cohen <sup>79</sup> (1925) . . . . .	1	Lumbar puncture	Sterile spinal fluid in 1 month
Valls, Palazzo and Ottolenghi <sup>81</sup> (1928)	1	Gunshot wound in lower spine	Recovery
Vaughan, Beck and Shelton <sup>85</sup> (1931) . . . . .	1	? Focus in nose with direct extension or bacteremia; possibly from lumbar puncture ?	Recovery in 1 month Received autogenous vaccine treatment Recovery in 2 months
Ghon <sup>86</sup> (1932) (observed in 1905) . . . . .	1	Infected spina bifida	Death
Shrewsbury <sup>87</sup> (1934) . . . . .	1	Spinal anesthesia	Recovery in 6 weeks
Bhatnagar <sup>88</sup> (1934) . . . . .	1	Spinal anesthesia	Death in 7 days
Evans <sup>88</sup> (1936) . . . . .	3	Lumbar puncture	Recovery in 1 case Death in 2 cases
Ibrahim <sup>91</sup> (1937) . . . . .	1	Lumbar puncture	Recovery
Berger <sup>93</sup> (1938) . . . . .	1	Lumbar puncture	Recovery
Iwasake and Motinaga <sup>98</sup> (1939) . . . . .	1	Pneumoencephalography	Not known
Wise and Musser <sup>94</sup> (1939) . . . . .	6	Lumbar puncture (contaminated Hg manometer)	2 deaths 4 recoveries
Kerman, Perlstein and Levinson <sup>99</sup> (1943) . . . . .	1	Pneumoencephalography	Death
Botterell and Magner <sup>101</sup> (1945) . . . . .	11	Penetrating head wounds (during Normandy campaign). Six from contaminated penicillin	9 deaths 2 recoveries
Evans, F. T. <sup>100</sup> (1945) . . . . .	2	Spinal anesthesia	Death in both

(and intrathecally).<sup>94</sup> With the addition of these compounds it would seem that the prognosis is somewhat improved. The mortality rate was 55 per cent (of forty). Of those thirty-two cases resulting from lumbar puncture, spinal anesthesia, etc. twelve died, a mortality rate of 39 per cent (of thirty-one—outcome not known in one).  
As seen on Chart B there have been twenty-eight cases reported in which the diagnosis of *Bacillus pyocyaneus meningitis*

*secondary to a focus elsewhere* seemed reasonably certain. To this we add one case (Case H. B.). There were six instances of infection of newborn infants, presumably through the umbilicus. Two of the adult cases had an associated endocarditis.<sup>50, 53</sup> As would be expected where there was usually a primary disease, in itself grave, and where the meningitis was simply a terminal or additional complication, the prognosis is much worse. The mortality in this group was at

## CHART B

SUMMARY OF CASES REPORTED IN THE LITERATURE OF *B. PYOCYANEUS* MENINGITIS SECONDARY TO A FOCUS ELSEWHERE

Author	Age	Primary Condition	Outcome	Other Findings
Kossel <sup>59</sup> (1893) . . . . .	6 weeks	Otitis media	Death	At autopsy, <i>B. pyocyaneus</i> isolated in pure culture from meninges and heart blood and in combination with pneumococci from middle ear and lung
Pesina and Honl <sup>60</sup> (1894) . . . . .	Adult		Death	<i>B. pyocyaneus</i> and Friedländer's bacillus isolated from purulent meningeal exudate
Councilman, Mallory and Wright <sup>61</sup> (1898) . . . . .		No information		
Perkins <sup>19</sup> (1901) . . . . .	25	Abortion followed by sepsis	Death	<i>B. pyocyaneus</i> isolated from uterus with <i>Staphylococcus aureus</i> . <i>B. pyocyaneus</i> isolated in pure cultures from liver and meninges. Fibrino-purulent endometritis also present
Berka <sup>62</sup> (1903) . . . . .	52	Pneumonia (?)	Death	
Horder <sup>63</sup> (1904) . . . . .		Chronic otitis media	Death	Pure cultures. <i>B. pyocyaneus</i> from both middle ears, lungs and meninges
Rolly <sup>55</sup> (1906) . . . . .	28	Abortion followed by sepsis	Death	Acute endocarditis of mitral valve due to <i>B. pyocyaneus</i> (old rheumatic mitral stenosis)
Hubener <sup>64</sup> (1907) . . . . .	18	Pelvic abscess	Death	Renal abscess
Benfey <sup>65</sup> (1907) . . . . .	8 days	Infection of umbilicus	Death	
Lagniffoul, Bousquet and Roger <sup>66</sup> (1910) . . . . .		Sepsis resembling typhoid fever	Death	
Fraenkel <sup>68</sup> (1912) . . . . .	23	Sepsis without obvious focus	Death	No symptoms of meningitis. <i>B. pyocyaneus</i> cultured from brain at autopsy
Gaethgens <sup>69</sup> (1914) . . . . .		Tuberculous meningitis	Death	<i>B. pyocyaneus</i> cultured from brain at autopsy. <i>B. pyocyaneus</i> may have been introduced by lumbar puncture
Fraenkel <sup>2</sup> (1917) . . . . .	1	Chronic otitis media	Death	Infection of pharyngeal mucous membrane and cecum
Canelli <sup>72</sup> (1919) . . . . .	2½ months	Enteritis; sepsis	Death	Sibling also died with <i>B. pyocyaneus</i> sepsis a few days before
Dudden <sup>73</sup> (1922) . . . . .	3½	Sepsis, possibly from focus in middle ear	Death	
Neal <sup>76</sup> (1924) . . . . .	7	No details given	?	
Kliew and Koch <sup>78</sup> (1924) . . . . .	4	Stomatitis	Recovery	
Chiari <sup>80</sup> (1926) 3 cases . . . . .	Under 10 days	Probably infection of umbilicus	Death in all three	All had purulent pericarditis. <i>B. pyocyaneus</i> observed in intestinal contents of one infant (? portal of entry)
Gaucheraud and Pigeaud <sup>82</sup> (1928) . . . . .	Newborn	Infection of umbilicus	Death in 37 days	Mother at birth had septic endometritis with infected amniotic fluid
Leadingham <sup>83</sup> (1930) . . . . .	20	No obvious <i>B. pyocyaneus</i> infection	Death	<i>B. pyocyaneus</i> from heart blood at autopsy. 3 month pregnancy. Diagnosed as "toxic encephalitis." Culture from brain and meninges sterile. No histological evidence of meningitis

CHART B.—(Continued)

Author	Age	Primary Condition	Outcome	Other Findings
Baumeister <sup>84</sup> (1931) . . . . .	24	Sepsis without obvious focus	Recovery after prolonged illness	Hemorrhagic lesions on the mucous membranes of the mouth, and on the skin
Bezi <sup>37</sup> (1933) . . . . .	2	Otitis, mastoiditis, lat. sinus thrombosis, sepsis	Death	Ecthyma gangrenosum. Gastrointestinal and pulmonary lesions
Neih <sup>90</sup> (1936) . . . . .	13	Mastoiditis with extension to the meninges	Death	
Roberts and Belsey <sup>92</sup> (1937) . .	31	Secondary infection of tuberculous empyema cavity with bacillus pyocyaneus (with bacteremia presumably)	Recovery	
Slutsky and Matlin <sup>95</sup> (1939) . .	49	Sepsis with the focus in the right kidney	Death	
Allin <sup>96</sup> (1941) . . . . .	Newborn	Infection of umbilicus	Death in 6 days	Intracranial hemorrhage. Congenital atelectasis of the left lung
Kraus and Hunter <sup>97</sup> (1941) . .	Newborn	Probably infection through umbilicus. Mother had enteric infection with chills and fever and diarrhea with <i>B. pyocyaneus</i> in stools while in labor	Death in 20 hours	Generalized macular rash at birth
Moragues and Anderson <sup>50</sup> (1943).	66	Infection of genitourinary tract	Death	Diabetes mellitus. Acute <i>B. pyocyaneus</i> endocarditis of mitral valve

least 86 per cent. The treatment has generally been unavailing, though recently sulfonamides and streptomycin have been used. When employed in the treatment of meningitis, streptomycin should be given intrathecally as well as systemically in large doses.

*B. pyocyaneus* has also been implicated as the cause of rhinitis and hemorrhagic meningitis in pigs.<sup>104a</sup>

*B. Brain Abscess.* There are only three reports concerning brain abscess due to *B. pyocyaneus* in addition to that of Botterell and Magner.<sup>101</sup>

1. Galavotti<sup>102</sup> described a two and one-half-year-old child who had convulsions every one or two months for eighteen months, with right hemiparesis and evidence of pronounced increase in intracranial pressure. At autopsy three communicating abscesses each 3 to 4 cm. in diameter were

found in the left hemisphere, as well as suppuration of both choroidal plexuses. The pathogenesis in this case was not clear although the wall of one of the abscesses was subjacent to a forceps scar. There was no history of sepsis and no fever.

2. Bocchini<sup>103</sup> described a two and one-half-month-old infant with bilateral abscesses of the anterior part of the choroid plexuses with extension into the adjacent walls of the ventricles. There was a short period of fever at the age of fifteen days; following this the main symptoms were those due to the rapidly increasing hydrocephalus.

3. The report of Cianci<sup>104</sup> was primarily concerned with the bacteriology of a cerebral abscess, and no details are given other than that *B. pyocyaneus* was recovered in pure culture and that there was a preceding acute otitis media.

## ARTHRITIS AND OSTEOMYELITIS

Cases of arthritis and osteomyelitis due to the *B. pyocyaneus* have been so rarely reported that brief summaries of the eight known cases (and one highly doubtful one) are appended. Two other cases<sup>47,143</sup> have been mentioned about which there are no details available. In seven instances it seemed highly probable that the involvement was metastatic, but Schein's case<sup>110</sup> was the only one in which positive blood culture proved this supposition.

Perkins<sup>19</sup> described a case of a thirty-year-old man who had pneumonia and evidence of fluid in the left pleural cavity. Later an abscess about the left seventh rib and acute purulent arthritis of the left elbow developed. Thick, greenish foul-smelling pus from which *B. pyocyaneus* was isolated was drained from both of these locations. On resection of the rib in the abscess floor there was no apparent connection between the abscess cavity and the pleural cavity. The patient died a short time later; there was no autopsy.

Waite's case<sup>3</sup> was that of a twenty-year-old female who had sudden onset of chills and high fever followed by intense pain and much swelling of one knee joint. Ten days after the onset a portion of the head of the tibia was resected. In the joint was a large amount of pus from which *B. pyocyaneus* was isolated in pure culture. Part of the tibia and the patella were necrotic. After two weeks in a cast a mid-thigh amputation was performed because of progressive infection of bones and soft parts. The patient improved rapidly and was discharged in two weeks. There was no mention of the origin of the infection.

Grove's case<sup>105</sup> was that of an eight-year-old boy who contracted secondary infection with *B. pyocyaneus* after operation for tuberculosis of the left hip joint. During a septic course of approximately two months' duration he developed purulent arthritis

of the right thumb and of the right hip joint. He was treated with autogenous vaccine to which the author attributes his rapid recovery. Although *B. pyocyaneus* was obtained only from the original site of infection (the other sites were not cultured), it is quite likely that the other suppurative foci were metastatic.

Pinelli<sup>106</sup> described a case of an eight-month-old baby who had fever of unknown etiology for six days at the age of six months. During the month before admission the child had been pale and sickly and had fever ranging from 38° to 39°c. and night sweats. The baby cried every time her shoulder was touched and avoided moving the left arm which was immobile and semi-flexed. Aspiration of the red and fluctuant shoulder joint produced 6 cc. of turbid, thin, odorless, slightly greenish pus from which *B. pyocyaneus* in pure culture was isolated. A few days later aspiration was repeated and vaccine therapy by intramuscular injection was begun. Only one other aspiration was necessary and recovery was rapid with normal function of joint restored.

Melina<sup>107</sup> described a case in a ten-year-old girl whose illness began with pain in the right hip and fever as high as 40°c. Later chills, intermittent fever, sweats and dry cough were persistent. Twenty days after onset a right thoracentesis produced 70 cc. of yellow-green serous fluid which was not cultured. One month after onset signs of the right pleural effusion persisted. Atrophy of the right hip was present and there was pain over the greater trochanter and sciatic region. X-ray revealed much destruction of the head of the right femur with involvement of the ischium and detachment of the head of the femur from the acetabulum. Aspiration of the hip produced slightly purulent serosanguineous fluid from which the *B. pyocyaneus* was isolated in pure culture. Her condition remained stationary

despite vaccine therapy and was unchanged when her parents took her home six weeks after onset of the illness.

Bishop<sup>108</sup> described a case of osteomyelitis and arthritis in a three and one-half-year-old boy. *B. pyocyaneus* infection in an area of first and second degree burn of the right leg and foot was followed by multiple subcutaneous abscesses and pyarthrosis of the right ankle joint with x-ray evidence of beginning destruction of the lower tibial epiphysis. After incision and drainage, he recovered rapidly. Fifteen months later he was re-admitted with recurrent inflammation of the right ankle joint associated with fever and night sweats. On incision and drainage of the joint, *B. pyocyaneus* was found in the pus. Autogenous vaccine was given. By the thirtieth day after admission the wound was well healed.

Bormioli<sup>109</sup> described an unusual case of acute osteomyelitis of the sternal manubrium which was considered to be the result of metastasis from a large furuncle on the right arm. (No cultures reported from the boil.) Following removal of the sequestrum which consisted of nearly the whole manubrium recovery was rapid. *B. pyocyaneus* was isolated in pure culture from the area of osteomyelitis.

Schein<sup>110</sup> reported a case of a fifty-six-year-old man who was cystoscoped because of bilateral renal lithiasis. This procedure was followed by chills and fever, prostration and delirium. From the urine a pure culture of *B. pyocyaneus* was grown. Blood culture was sterile. He was given a total of 27 Gm. of sulfanilamide for a period of nine days with improvement of symptoms and subsidence of fever. Soon after discontinuing the medication the patient noted pain and tenderness over the lower dorsal segments of the spine and the return of fever, 102 to 103°F. daily. The urine continued to yield *B. pyocyaneus* on culture. Blood culture revealed *B. pyocyaneus* on the thirtieth

hospital day. Sulfanilamide was again given; this time for six days, a total of 34 Gm. Temperature subsided and remained normal. Seven weeks after onset of sepsis x-ray evidence of osteomyelitis of the seventh and eighth dorsal vertebrae was obtained. There were also suggestive findings of a soft tissue abscess in the adjacent mediastinum. Further treatment consisted in the application of a plaster jacket. Convalescence was prolonged (about one year), but was uneventful. A year later culture of the urine still showed *B. pyocyaneus*.

The case reported by Fiset<sup>111</sup> was that of a seventy-two-year-old farmer who had suffered from progressive "chronic articular rheumatism" for ten years. He had anorexia and alternating constipation and diarrhea. There was slight periarticular edema, muscular atrophy in the limbs, and a "light deforming hypertrophy of the small articulations, mainly fingers." There was a low grade fever, 99° to 100°F. *B. pyocyaneus* was cultured in "striking abundance" from the stools. The patient's serum agglutinated the organism in dilutions of 1-600 (fifty-one controls had no higher titer than 1-20). It was considered that he suffered from intestinal infection with *B. pyocyaneus*, and that the arthritis was "a part of the picture." He was treated with vaccine by mouth for three months, at the end of which time the agglutination titer was 1-1100. After fifteen days he was asymptomatic. He had no relapses for three years.

From this report the causal relationship of the *B. pyocyaneus* to the arthritis is not clear. There was no suppuration of the joints, and it was not proved that there were any intestinal lesions. It is not clear why a vaccine given by mouth should have any effect on an infection of the gastrointestinal tract.

Other reports of osteomyelitis include one case with vertebral involvement<sup>47</sup> and one case (location not stated) inadequately

treated with streptomycin reported by Herrell and Nichols.<sup>143</sup> No details are given in either of these reports.

#### INFECTIONS OF THE EYE: CORNEAL ULCER

Involvement of the eye with *B. pyocyaneus* usually takes the form of a corneal ulcer, although the cases of necrosis of the eyelids,<sup>2,31</sup> dacrocystitis,<sup>112</sup> conjunctivitis<sup>113</sup> and punctate keratitis<sup>114</sup> are notable exceptions. Despite its rarity, it forms an important entity because the usual course without treatment, or with only local measures, is that of progressive extension of infection into the other parts of the eye, leading to loss of the globe.<sup>115</sup> *B. pyocyaneus* is said to be the most virulent organism that attacks the cornea; infection leads to panophthalmitis<sup>124,133</sup> even more certainly than with the streptococcus, staphylococcus or pneumococcus. When ulceration occurs, it almost invariably follows trauma to the cornea due to the presence of a foreign body or its removal; the organisms are not infrequently introduced through the use of contaminated solutions of fluorescein<sup>120</sup> or boric acid<sup>132</sup> instilled after such manipulations. *B. pyocyaneus* will live in 4 per cent boric acid.<sup>132</sup>

The first recognized case of corneal ulcer was reported by Sattler<sup>116</sup> (1891). Compilation of reported cases in the review papers by Mauersberg,<sup>117</sup> Jacobi,<sup>118</sup> Morelli<sup>119</sup> and Joy<sup>115</sup> totaled sixty-four cases in 1942. Since that time, sixteen more have been added, making a total of eighty cases. This latter group is tabulated in some detail in the accompanying table (Chart c) because of the good results which have been brought about by the use of the sulfonamide drugs, particularly sulfapyridine, sulfadiazine and sulfanilamide. This is in contrast to older methods of treatment.

*Treatment.* The traditional vigorous local therapy consisting of hot packs, atropinization, irrigation and instillation of various

antiseptics, incision of the cornea and actual cautery of the ulcerated area, was almost uniformly unsuccessful in preventing loss of the eye. Experimentally, twenty-four to thirty-two hours after inoculation of the cornea of the rabbit, the presence of bacilli in normal corneal tissue often far removed from the site of inoculation could be demonstrated.<sup>125,126,127</sup> Presumably this was brought about by lymphatic spread and affords a ready explanation for the inefficacy of local treatment which has so often been observed clinically.

The demonstration, also in rabbits, that the sulfonamides penetrated into the tissues of the eye in significant amounts<sup>128</sup> has pointed the way to a rational form of treatment. Sulfapyridine and sulfanilamide attain higher concentrations in the aqueous and the cornea than sulfadiazine and sulfathazole.<sup>129,130</sup> For this reason, Joy<sup>115</sup> used sulfapyridine in the therapy of experimental infections with excellent results, although his dosages were so high as to make them inapplicable to man. This work, however, has had ample confirmation clinically.<sup>120,124,131</sup>

von Sallman showed<sup>121</sup> that much higher levels of the sulfonamides could be obtained in the anterior segments of the eye by iontophoresis than with other methods. Sodium sulfadiazine entered in larger amounts than any of the other sulfonamides, and this method was superior to other means of administration of this drug and to other local treatment. However, the best results were obtained by a combination of iontophoresis, local application of sulfadiazine powder and oral administration of sulfadiazine. He treated two patients each with a large corneal ulcer, iritis and high hypopyon with this combined therapy with good final results in both.

Although nothing further has been published by von Sallman on this subject the iontophoretic method, particularly when combined with other sulfadiazine therapy,

## CHART C

SUMMARY OF CASES OF CORNEAL ULCER DUE TO *B. PYOCYANEUS* WHICH HAVE BEEN REPORTED SINCE TREATMENT WITH THE SULFONAMIDES HAS BEEN USED

Year	Author	No. of Cases	Initial Injury to Cornea	Treatment	Outcome	Remarks
1941	Lepard <sup>120</sup>	3	Unstated types of foreign body (industrial workers)	Local treatment Local plus sulfanilamide late in the course of disease Local plus sulfapyridine	Enucleation Enucleation  Thin scar at site of ulcer. Vision 20/20 25 days after injury	Total corneal involvement  B. pyocyaneus cultured from fluorescein solution, used in eye
1941	Rudolph (discussion under Lepard)	2	Not stated	Sulfathiazole by mouth. 5% sulfathiazole locally. "Delimiting keratotomy" 10th day. Sulfacetamide 4 Gm. late in course of disease Glacial acetic acid applied to ulcer. Sulfacetamide 4 Gm. late in course of disease. Corneal paracentesis 8th day	Evisceration   Evisceration	Panophthalmitis   Ulcer spread over entire cornea
1941	Cooper (discussion under Lepard)	4	Unstated types of foreign body (industrial workers)	Sulfathiazole 2 days, sulfapyridine after 2nd day  Sulfathiazole 1 day, sulfapyridine after 1st day. Local cautery 14th day  Sulfathiazole 1 day, sulfapyridine after 1st day Sulfathiazole 1 dose, sulfapyridine after 1st dose	Progress of infection checked  Ulcer healed slowly. Irridec-tomy 2 months later. Final vision 20/60 with correction Enucleation Large corneal scar without useful vision	Secondary glaucoma developed. Eye later enucleated. Apparently healing ulcer spread widely after cautery   Slow progression to panophthalmitis
1942	von Sallman <sup>121</sup>	2	Not stated	Oral administration of sulfadiazine, sodium sulfadiazine solution by iontophoresis into anterior eye, and local application of sulfadiazine powder	"Good final results" in both	Both ulcers large with hypopyon and iritis
1942	Solomon <sup>122</sup>	1	Sand spur	Local treatment with stropine, zinc sulfate, hot applications, etc. Foreign protein injections ("Lactogen"). On 40th day, neoprontosil	Thin scar over pupil. Some useful vision remained	Rapid improvement after neoprontosil begun
1943	Goldberg <sup>123</sup>	1	Not stated	Sulfathiazole, 4 Gm. daily by mouth	Cured. Vision 20/20 bilaterally	Multiple superficial ulcerations bilaterally. Treatment begun early, before results of cultures known
1943	Brown <sup>124</sup>	3	Not stated	Sulfadiazine by mouth  Sulfathiazole by mouth  Sulfapyridine by mouth (All had local treatment)	Enucleation  Enucleation  Large corneal scar. Vision 10/400	Progressive infection Progressive infection Healed completely in two months

would seem to be the method of choice. When facilities for this type of treatment are not available, either sulfapyridine or sulfanilamide by mouth or parenterally is the drug of choice. Nothing has been published concerning the effect of streptomycin on this type of pyocyaneus infection, but it is quite likely that this agent will also be effective in treatment of corneal ulcers.

#### INFECTIONS OF THE EAR

*A. Otitis Externa.* (See also section on skin infections). In the tropics, especially during the rainy season, inflammation of the auricle occurs rather commonly.<sup>134</sup> There is pain, often excruciating, a seropurulent discharge from the ear with partial or complete occlusion of the meatus, low-grade fever and regional lymphadenitis. The process may spread peripherally to involve the skin over the mastoid and face.<sup>135</sup> Only rarely does the inflammation proceed to "boil" formation. The pronounced increase in incidence during the wet season, at which time "prickly heat" is also quite common, causes the use of the term "hot-weather ear." This accents the strongest etiological factor; the constantly moist, macerated skin in areas of contact is especially susceptible to infection.

The *B. pyocyaneus*, either in pure culture or associated with *Corynebacterium ceruminis* is found in the discharge in many cases.<sup>134</sup> Other instances are due to fungi.

In many patients the infection is difficult to cure and recurrences are frequent. The most important consideration is to keep the ear dry; as a corollary to this, it is necessary to avoid ear plugs or other devices worn while bathing which promote maceration of the epithelium. Local therapy has consisted of heat, boric acid lotion, boriodine powder and phenyl mercuric nitrate 1:1250 in 95 per cent alcohol.<sup>136</sup> Vaccine has also been used with some good results. It would be expected that the sulfonamides

and streptomycin would be as efficacious here as elsewhere.

*B. Otitis Media.* In the usual instance in which *B. pyocyaneus* is cultured from a draining ear, the process is a chronic one and the organism obviously a secondary invader.<sup>31</sup> An occasional example of apparently primary otitis media has also been reported.<sup>59</sup> The presence of bacilli in large numbers in the pharyngeal exudate in these cases affords a logical explanation as to the pathogenesis. Mastoiditis and thrombophlebitis of the lateral sinus with septicemia<sup>37,90</sup> are uncommon complications. Six of the reported cases of meningitis<sup>2,37,59,63,73,90</sup> were preceded by otitis media; direct extension could not be demonstrated in some cases in which bacteremia was present<sup>37,90</sup> so it is likely that these instances were due to blood-borne metastases.

#### RESPIRATORY TRACT

Infection of the respiratory tree is relatively unimportant in pyocyaneus infection because it is infrequently involved primarily and is rarely the portal of entry for the organism.

Kossel<sup>59</sup> (1894) described two fatal cases in children in both of whom there was otitis media, in one associated with purulent pansinusitis, and in the other with purulent rhinitis, laryngitis, tracheitis and enteritis.

Ulceration of the pharynx, tonsils and buccal mucosa with formation of an extensive necrotic membrane simulating that in scarlet fever or diphtheria has already been described as part of the lesions of the gastrointestinal tract. Smaller ulcerations involving the larynx, trachea and bronchi have been discovered at autopsy by Fraenkel,<sup>2</sup> Bezi<sup>37</sup> and Rolly.<sup>55</sup> In one instance these occurred in a patient with pulmonary tuberculosis who also had tuberculous ulcers of the larynx and bronchi, but the two were easily differentiated by the characteristic finding in the former of masses



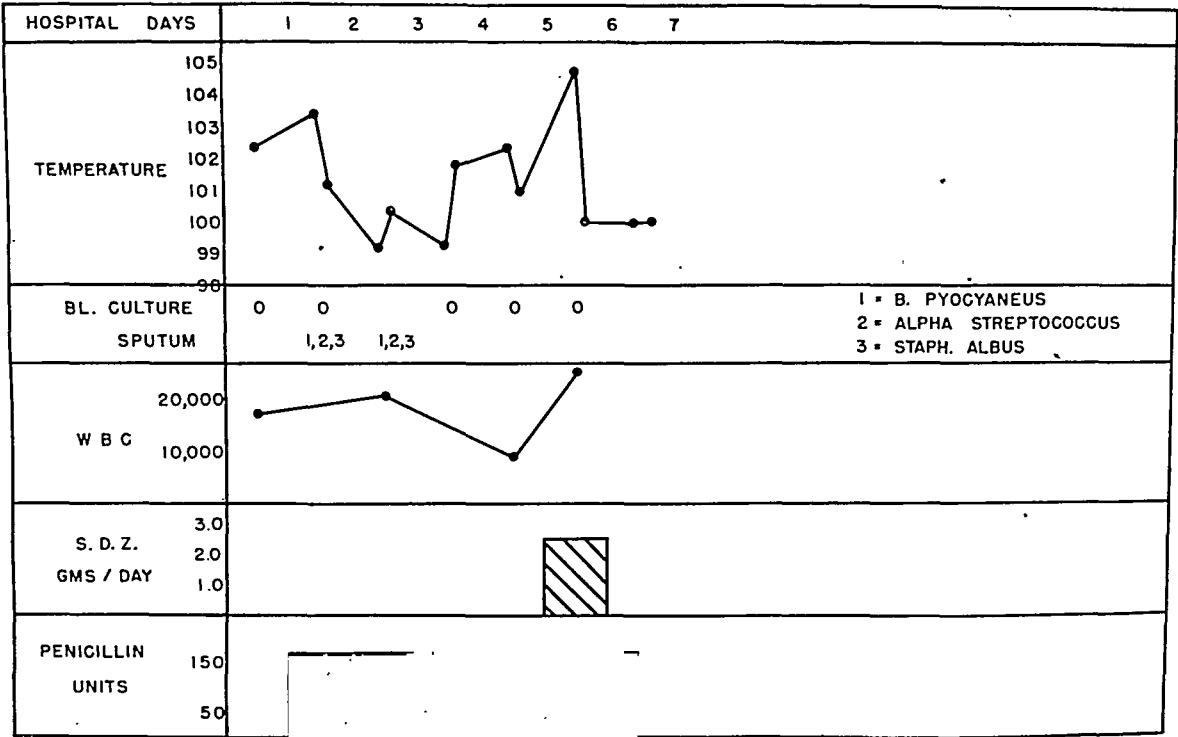


FIG. 7. Case x. Rapidly fatal course with treatment of pyocyaneus pneumonia and empyema with penicillin and sulfadiazine.

of gram-negative slender bacilli in the blood vessel walls and by the presence of *B. pyocyaneus* in the blood terminally.

Primary invasion of the lung, with pneumonitis as the principal illness, has been rarely seen. Fraenkel's case<sup>2</sup> of a twenty-year-old soldier whose lung abscess drained spontaneously into a bronchus and was followed by long-continued expectoration of thin, fetid, purulent sputum containing *B. pyocyaneus* in large numbers is an example. The clinical diagnosis in this instance was not confirmed as there was no surgery performed. Our Case x is another rare instance of primary pneumonitis.

In the cases described as bronchopneumonia,<sup>34,37</sup> inadequate histological detail prevents judgment as to whether or not the processes were metastatic or ectogenous. The former type of lesion is the only one recorded in the reports which contain detailed microscopic accounts.<sup>2,17,26</sup> Thus in many cases of sepsis (Case 1), the lung

exhibits multiple 5 to 10 mm. areas of necrosis with peripheral hemorrhage in the centers of which the involved arterioles can be seen. Throughout the necrotic areas and in the walls of the blood vessels, large masses of slender gram-negative rods can be characteristically demonstrated.

The case described below was apparently primary pneumonitis (Case x), a very unusual condition. The relation of the aspirated lipoid material to the terminal illness is not clear because it was obvious that the pneumonitis caused by this material was quite old. It is probable that it resulted from the use of oily nose drops in the treatment of sinusitis.

CASE x. This patient had bilateral pneumonia due to *B. pyocyaneus* followed by empyema. (Fig. 7.) Penicillin and sulfadiazine therapy was employed and his course was rapidly downhill.

G. H. was a seventy-three-year-old, white male account collector who was admitted com-

plaining of cough and left pleuritic chest pain. Acute frontal sinusitis sixteen years prior to admission was followed one year later by a radical operation on the left frontal sinus. Since this time he had had recurrent episodes of purulent nasal and postnasal discharge and occasional spontaneous epistaxes. There had also been a chronic, non-productive cough for several years.

Acute rheumatoid arthritis, involving the hands, elbows, knees and feet occurred ten years prior to admission. During the five years prior to admission, the process had been quiescent, but some difficulty in walking had persisted due to the deformity.

Four days prior to admission a nosebleed occurred. A few hours later a cough began which became productive of yellow sputum. Pain on coughing or deep breathing was noted over the left anterior chest twenty-four hours later; oral temperature was 101.4°F. The following morning, two days prior to admission, he was afebrile and felt improved. During these next two days, however, the fever returned, the cough became worse and the sputum assumed a rusty tinge. There were no chills or chilly sensations.

Physical examination revealed the temperature to be 103.8°F., pulse 135, respiration 34, blood pressure 100/65. The patient was a well developed, elderly man, acutely ill but not in great distress. The pharynx was diffusely reddened and there was a purulent postnasal discharge. Respirations were moderately rapid and shallow. There was a lag in respiratory excursion on the left. There was increased tactile and vocal fremitus, dullness to percussion and bronchovesicular breath sounds over the left base, posteriorly. Coarse, moist inspiratory râles were heard over all lung fields, more prominently on the right. Heart and abdomen were normal. There were deformities of the hands and feet characteristic of chronic rheumatoid arthritis in a quiescent stage.

Laboratory examination showed the following: Blood Hinton was negative. Urine was normal on admission and subsequently also, except for slight microscopic pyuria and hematuria while there was an inlying catheter in the bladder. Hemoglobin was 11 Gm. per cent on admission; two days later, after a 500 cc. transfusion, hemo-

globin was 15 Gm. per cent and hematocrit 46.5 per cent. Total white blood count was 17,600 per c. mm. on admission, 20,200 per c. mm. on the second hospital day, fell to 9,000 on the fourth day, but rose again to 25,150 on the fifth day (day before death). Blood non-protein nitrogen was 57 mg. per cent on admission.

Although there were gram-positive cocci seen in the stained smear of the sputum on admission, culture revealed that the predominant organism was *B. pyocyaneus* on both the first and second hospital days. Sputum contained also small numbers of alpha streptococci and *Staphylococcus albus*. Blood cultures on the first, second, fourth and fifth days were sterile.

Electrocardiogram taken on the third day showed a sinus arrhythmia, rate 120 per minute, low voltage and slurring Q-R-S complexes, and inversion of T<sub>2</sub> and T<sub>3</sub>, normal axis. Five hours later there was uncontrolled auricular fibrillation with a ventricular rate of around 180 per minute.

Chest x-ray on admission revealed diffuse density throughout the left lung field, with a localized area of homogeneous density at the base of the upper lobe and a similar linear area at the base of the lower lobe. There was mottled density throughout the right lung field. There was an increase in the transverse diameter of the heart. A bedside x-ray on the fourth day showed insignificant resolution of the bilateral pneumonic process.

Penicillin, 20,000 units every three hours intramuscularly, was begun on admission and continued until death. Oxygen by B.L.B. mask was started later on the first day. A 500 cc. whole blood transfusion was given also during the first day. There was a large amount of thick, tenacious, mucopurulent sputum produced, which required frequent suctioning to prevent obstruction of the trachea. On the second day, a pleural friction rub was heard at the base of the right axilla. Despite these findings, he appeared to improve slowly during the first three days in the hospital. The temperature gradually fell to normal, and regression of the signs of consolidation on the left occurred, though there then appeared signs of dullness and bronchial breathing at the right base, and the friction rub persisted in this location. During the third day he developed

auricular fibrillation with a rapid ventricular rate, which was not slowed markedly by administration of 1.6 mg. of lanatoside C. Later that day, he suddenly became cyanotic and cold, and there was extreme dullness with absent breath sounds over most of the right lung, posteriorly, with deviation of the trachea to the right. These phenomena were almost completely reversed in a short time after a catheter had been introduced into the trachea and large amounts of secretions aspirated. His temperature slowly rose and during the fourth day stayed around 102°F. rectally. At bronchoscopy it was demonstrated that the bronchi to the right lung were almost completely occluded by secretions, and marked improvement in respiratory exchange seemed to follow their removal by this method. However, physical signs of absolute flatness below the seventh rib laterally on the left, with a friction rub in this location as well as on the right were noted. During the early part of the fifth day, the temperature was 104 to 105°F. rectally. He was given 2.5 Gm. of sodium sulfadiazine intravenously, and 3,000 cc. fluids intravenously. During the next twelve hours there was a steady fall in temperature to normal. On the morning of the sixth day, after appearing much improved, he suddenly became cyanotic and died in a short time, apparently of obstruction of his airway.

**GROSS PATHOLOGY.** *Pleural Cavities:* The left pleural cavity contained 1,000 cc. of thin, turbid, blood-tinged fluid. The left lower lobe appeared collapsed and atelectatic. There were dense fibrous adhesions binding the base of the left lung to the parietal pleura and the dome of the diaphragm. On breaking through these adhesions, a large amount of purulent fibrin-filled fluid was evacuated. The surface of the pleura was ragged and yellow with a considerable amount of inflammatory exudate, which was contained in the walled-off pockets.

The right pleural cavity was largely obliterated by numerous fibrous adhesions and contained about 50 cc. of yellow, turbid fluid. There were numerous adhesions, between the pleura and the pericardium. The pleural surface was grayish-pink and somewhat ragged where the adhesions were torn.

*Lungs:* The right lung weighed 920 Gm. About 3 cm. above the base of the lung, the surface was

puckered and fissured as if drawn in by a tight constriction. This area was hard in consistency and somewhat nodular. There was rather firm consolidation of the entire right lower lobe, and the lower 2 cm. of the right upper lobe. The right middle lobe was less densely consolidated, but was definitely firmer than normal. The pleural surfaces were smooth, moist and dark grayish-pink in color. There were many fine adhesions between the visceral and parietal pleura, particularly between the pleura and the pericardium. On cutting through the right lower lobe in the constricted area, there were numerous nodular areas, grayish and grayish-white in appearance, in some places having the gross characteristics of caseation necrosis. These areas were moderately well circumscribed but were numerous and occupied the main portion of the lower third of the right lower lobe. The remainder of the right lower lobe and the right middle and the lower portion of the right upper lobe showed moderately dense consolidation. Only the apex of the right upper lobe showed the normal crepitation and aerated appearance. The bronchi were patent and contained no exudate. The bronchial and hilar lymph nodes were normal in size and moderately anthracotic.

The left lung weighed 560 Gm. The base of the left lung was very adherent to the dome of the diaphragm with numerous fibrous adhesions. There were fibrinous and easily torn fibrous adhesions along the entire surface of the left lower lobe, which was rubbery in consistency. Aside from the adhesions, and the area of inflammatory exudate around the base, the pleura was smooth, moist and grayish-pink in color. The left upper lobe showed some crepitation and aeration. However, the left lower lobe was completely atelectatic. On cut surface the left lower lobe was dense, dark red in color and rubbery in consistency. The left upper lobe was moderately well aerated and grayish-pink in color. The bronchi were patent and showed no exudate. The arteries and veins showed no antemortem thrombi or emboli in either lung.

*Spleen:* The spleen weighed 220 Gm., was firm and moderately engorged. On the surface there were several small, slightly pale, depressed areas which had the appearance of infarcts.

*Liver:* The liver weighed 1,440 Gm., was very firm and the yellowish-brown color on cut surface was distinctly pathological. Over the anterior surface of the right lobe there was an area of fibrous thickening in the region of the attachment of adhesions to the diaphragm.

**MICROSCOPIC PATHOLOGY.** *Lungs:* The firm scarred area in the right lower lobe showed diffuse, chronic infiltration with fibrosis and foreign body giant cell reaction to fat. The normal pulmonary architecture in this area was completely obliterated. In the center of this region there was a cyst-like cavity filled with amorphous eosinophilic granular matter and round or oval vacuoles representing fat. This lesion was consistent with reaction to aspirated lipid material. In the remainder of the lobe there was pronounced diffuse acute purulent bronchitis and bronchopneumonia with the alveolar spaces and bronchioles filled with polymorphonuclear leukocytes and macrophages. In the exudate there were slender bacilli. There were many large fat vacuoles scattered through the areas of acute inflammation and contained in many of the macrophages. In the left lower lobe there was marked generalized congestion and partial atelectasis. There was only a small amount of purulent exudate in the bronchioles and alveoli, and much less acute inflammation than in the right lower lobe. Small numbers of bacilli and bacilli and cocci were seen in the exudate.

*Liver:* There was extensive central degeneration and necrosis of the liver cells with slight infiltration with polymorphonuclear leukocytes and macrophages. In one section frequently marked congestion and hemorrhage were associated with the focal lesions. No significant vascular lesions were found. No bacteria were present. In a broad zone beneath the capsule there was marked fibrosis extending into and replacing the parenchyma to a considerable degree. In this zone of fibrosis, proliferation of bile ducts and infiltration with chronic inflammatory cells were present.

*Spleen:* There was diffuse congestion and infiltration with polymorphonuclear leukocytes. There were numerous large, irregular areas of necrosis which were more densely infiltrated with acute inflammatory cells; some of these lesions were undoubtedly infarcts.

There was pronounced atheromatosis of the aorta. Generalized renal congestion was present.

*Bacteriology:* *Right lower lobe of lung:* *B. pyocyaneus*, *B. mucosus*, non-hemolytic staphylococcus aureus, and *B. coli*. *Left lower lobe of lung and left main bronchus:* *B. pyocyaneus*, non-hemolytic staphylococcus aureus, and *B. mucosus*.

*Final Pathological Diagnosis:* Diffuse bilateral bronchopneumonia and acute bronchitis (see bacteriology); bilateral empyema (pleural); atelectasis of the left lower lobe of the lung; lipid pneumonia, healed, right lower lobe of lung; central necroses of liver, marked, and acute splenitis and multiple infarcts of spleen.

#### TREATMENT

There is a wide variation in the spontaneous course of systemic infections depending upon many factors, such as presence of other serious disease, virulence of the organism, route of introduction of the organism, the location of foci and their accessibility to surgical drainage, presence of intravascular foci such as endocarditis, and lateral sinus thrombophlebitis. In general, however, when there is repeated or prolonged bacteremia, the outcome is fatal in untreated cases.

*Vaccines.* The principal agent used in treatment of all types of *B. pyocyaneus* infections until nine years ago was autogenous vaccine. Assay of the results is difficult, although in several<sup>35,105</sup> instances it apparently influenced favorably what seemed to be a generally downhill course. There are many more examples of failure of such treatment.<sup>2</sup> Since the introduction of the sulfonamides and streptomycin, it has seldom been used.

*Sulfonamides.* Since the report of Soeters<sup>137</sup> in 1937, describing the recovery from sepsis in a child treated with prontosil, the various sulfonamides have been extensively employed for all types of infections. The results have often not been dramatic, although these drugs undoubtedly repre-

sented a great improvement over other forms of therapy previously known, both in effectiveness and in ease of administration. The variation of *in vitro* sensitivity of strains of *B. pyocyaneus* isolated from untreated patients is considerable;<sup>115</sup> some strains are relatively resistant. Sulfadiazine is the sulfonamide of choice because of the low rate of toxic reactions, although the other members of the group are effective also. Under certain conditions in the treatment of corneal ulcer, sulfanilimide or sulfapyridine may be preferable because of their greater ability to penetrate into the tissues of the eye (see section on eye infections).

One should not lose sight of the few simple precautions necessary for protection of the patient during sulfonamide therapy. These include the maintenance of an adequate fluid intake so that the urinary output is at least 1,500 cc. daily, frequent estimation of blood sulfonamide levels and hemograms, and careful observation for other evidences of toxicity such as fever, rash or jaundice.

*Streptomycin.* Since the initial description of streptomycin by Schatz, Bugie and Waksman<sup>140</sup> in 1944 there have been few reports of its use in treatment of *B. pyocyaneus* infections in experimental animals<sup>141</sup> and in man.<sup>142,143</sup> The total of such cases treated in this institution is still small so that one can only gain some preliminary impression as to its effectiveness. Of the three patients with sepsis reported herein treated with streptomycin none survived. The presence of associated disease was a factor which influenced the outcome in each case. Again, there is great variation from strain to strain in sensitivity of the organism to streptomycin. Thus, in Case II (H. B.) whose organism was sensitive to 10 units per cc. the blood stream was sterilized without difficulty, while in Case III (C. L.) there was no effect on a bacteremia caused by an organism resistant to 500 units per cc. Both these patients died, although there can be

little doubt that under more favorable circumstances the treatment would have been curative in the former instance.

In the treatment of meningitis streptomycin should be administered intrathecally, 100,000 units daily, as well as intramuscularly. The therapy in Case II (H. B.), in whom meningitis certainly contributed to the fatal outcome, conceivably would have been completely successful if he had received the drug in adequate dosage directly into the spinal fluid.

CHART D  
CHANGES IN SENSITIVITY TO STREPTOMYCIN OF THE VARIOUS ORGANISMS CULTURED FROM PATIENTS DESCRIBED IN THIS REPORT

Case	Before Treatment	Following Treatment
II	<i>B. pyocyaneus</i> inhibited by 10 units/cc.	(Blood sterilized)
III	<i>B. pyocyaneus</i> resistant to 8 units/cc. (inhibited by 16 units/cc.)	Resistant to 500 units/cc.
IV	<i>B. pyocyaneus</i> inhibited by 12 units/cc.	Resistant to 50 units/cc.
VI	<i>B. coli</i> inhibited by 4 units/cc.	Resistant to 200 units/cc.
	<i>B. coli</i> inhibited by 8 units/cc.	<i>B. coli</i> resistant to 200 units/cc.
	<i>B. proteus</i> inhibited by 8 units/cc.	
VII	<i>B. pyocyaneus</i> inhibited by 12 units/cc.	
	<i>B. mucosus</i> inhibited by 12 units/cc.	
	<i>B. coli</i> inhibited by 8 units/cc.	<i>B. coli</i> resistant to 200 units/cc.
VIII	<i>B. pyocyaneus</i> inhibited by 12 units/cc.	
	<i>B. coli</i> inhibited by 8 units/cc.	
	<i>B. pyocyaneus</i> inhibited by 12 units/cc.	<i>B. coli</i> resistant to 50 units/cc. (Organism appeared during streptomycin treatment)

A mixed flora of gram-negative organisms is often seen in the superficial infections of the urinary tract which commonly occur following instrumentation. Streptomycin may be quite effective in eradicating the *B. pyocyaneus* from the urine although it usually is not uniformly successful in combatting all members of the group, (Cases VI, VII, VIII). However, the studies of Helmholz<sup>144</sup> show that some strains are among the most resistant of the organisms found in the urine. At least one of the mixture of organisms, usually *B. coli* in our experience, will often develop such pro-

nounced and rapidly increasing resistance to the agent that adequate treatment is not feasible. This factor is not as important with *B. pyocyaneus* as it is with *B. coli*, the resistance of which increases phenomenally during a short period of treatment. (Chart D.) This rapid change in susceptibility of the organism is not so evident in sulfonamide therapy, although it undoubtedly occurs to some extent. Thus such mixed infections will usually be greatly improved by elimination of some of the organisms, including *B. pyocyaneus* frequently, but will often not be completely cured. Three of the five cases reported here exhibited this phenomenon (vi, vii, viii) while in one (iv) the urine was completely sterilized, at least temporarily, and in another (v) the whole group was resistant. These patients received 1 Gm. daily in divided doses every three to six hours intramuscularly for totals of 4 to 11 Gm. (except iv who had massive doses).

It is apparent from this small number of cases that streptomycin is a valuable addition to the limited number of agents which are effective against this organism, and that it may prove on further trial to be just as effective as the sulfonamides, if not more so. The striking lack of the characteristic histological findings at autopsy in Cases ii and iv suggest that the streptomycin treatment exerted definitely beneficial effects even though these patients died. It is quite likely that strains which are resistant to one will be sensitive to the other so that the chances of cure in any infection are greatly enhanced by this addition.

*Urethane and Sulfanilamide Solution.* Recently good results have been reported in the treatment of local pyocyaneus infections with a solution of 10 per cent urethane and 1 per cent sulfanilamide applied directly to the areas every three hours. In a group of thirty-nine cases<sup>145</sup> there were fifteen in which the infections were caused primarily or in part by *B. pyocyaneus*, including

chronic leg ulcers, chronic decubitus ulcers, infected surgical wounds and two instances of infected empyema cavities. When combined with adequate surgical drainage and/or débridement application of the mixture caused a disappearance of this organism from the infected areas in two to four days in the great majority, including one of the two cases of empyema.

In one of our cases (Case i) who received such treatment of the large decubitus ulcers locally combined with débridement the local response was excellent, although the necrotic areas were so large and her general condition was so poor that the prognosis was hopeless from the start.

*Phenoxetol* ( $\beta$ -phenoxyethylalcohol). In 2.2 per cent aqueous solution this substance has given good results in treatment of infected burns and superficial wounds.<sup>146</sup> When applied as constant soaks wet once daily the *B. pyocyaneus* was usually eliminated from the wounds in less than one week. *B. proteus* was more resistant, although frequently the wounds were also sterilized of this organism after a longer period of treatment. There was no effect on the gram-positive flora.

*Acetic Acid.* In 1 to 2 per cent solution acetic acid has been successfully used for many years in the treatment of superficial infections due to *B. pyocyaneus*, although some of the newer substances may be more rapidly efficacious. Taylor<sup>147</sup> found acetic acid dressings and soaks much more effective than a number of other medicaments, including Dakin's solution, in wound infections, and Rank<sup>148</sup> as recently as 1940 preferred it for treatment of infected granulating areas to be skin grafted.

#### COMMENTS

From consideration of the data presented the pattern of pyocyaneus infections is distinct. The organism is a gram-negative bacillus commonly found on the human

skin and infrequently in the normal gastrointestinal tract. It lacks invasive properties, hence its usual rôle is one of a relatively avirulent contaminant especially in superficial wounds in which it produces a characteristic blue-green pus. Sepsis and other serious infections due to this organism are definitely rare. However, because of the widespread use at present of penicillin, which efficiently removes gram-positive organisms and apparently promotes uninhibited growth of this and other gram-negative bacilli, the incidence of such important infections seems to be increasing. Case II, III, IV, IX and X are examples in whom it is probable that treatment with penicillin may have produced conditions favoring *B. pyocyaneus* invasion, or at least conditions which were ideal for rapid spread of such infection once a foothold had been established.

In addition to the usual manifestations several unique features serve to differentiate septic infections due to *B. pyocyaneus* from other types of sepsis. They occur almost exclusively in infants and children and in debilitated adults. Without exception our cases were in this latter group. Highly characteristic is the tendency to vascular involvement with thrombosis and infarction, resulting in production of ulcerating gangrenous areas in the skin ("ecthyma gangrenosum") particularly in the perineal and axillary regions, and in all sections of the gastrointestinal tract. Cases I, II and III exhibited these typical lesions, respectively, in the stomach, on the skin and in the rectum. The skin lesions and the large rectal ulcer were especially striking.

*B. pyocyaneus* sepsis is almost uniformly fatal, probably because of several factors. One of these is the tendency to occur in infants and children and adults with chronic debilitating disease which is so clearly shown in the literature and in our several cases. It is not surprising that in such individuals

the mortality rate approaches 100 per cent; the almost universally fatal outcome is probably as much the result of the pre-existing disease as it is of the superimposed pyocyaneus infection. Corroborating this is the good prognosis in the rare cases of persistent bacteremia simulating typhoid fever which generally occur in healthy individuals.

A second consideration in the prognosis is the resistance—original or acquired—of the strain of organism to the available chemotherapeutic agents. In the sulfonamides and streptomycin we have two quite promising drugs. Yet there is a large variation from strain to strain in sensitivity to both these substances, and a fair proportion is initially resistant. The lack of susceptibility to the two agents does not necessarily overlap, however, and a particular organism may be sensitive to one and resistant to the other, or vice versa. What is probably of equal importance is resistance in an originally sensitive strain developing rapidly during treatment, particularly with streptomycin. (Chart D.) An extreme example of such an occurrence was seen in Case III. Although from this and other studies it is apparent that the tendency to rapid development of resistance is seen more commonly with other organisms such as *B. coli*, this factor must have been an important reason in the failure of treatment in Case III. This phenomenon is a well known one; it occurs with many organisms and all types of chemotherapeutic agents. It can readily be produced *in vitro* and is an example of the ease with which bacteria can adapt themselves to an unfavorable environment.

Treatment, in this as in other infections, should be undertaken with these facts in mind. Since exposure to sublethal concentrations of the agent produces optimum conditions for development of resistance in the infecting organism dosage from the beginning should be adequate. In treatment

of pyocyaneus sepsis with streptomycin this means an initial dosage of 4 Gm. daily in divided doses every three hours intramuscularly. In urinary tract and other local infections 2 Gm. daily may be sufficient, although a resistant organism may necessitate a larger dose. In case of lack of response the resistance should be checked again using a freshly isolated organism. While streptomycin is still being administered cultures should be repeated frequently, not only of the blood but also of the nose and pharynx and other possible foci in an effort to detect in its incipency a possible predominance of gram-positive pathogens. The development of serious infections with *gram-positive* organisms is already being noted in patients treated with streptomycin alone<sup>149</sup> and should be searched for carefully. In the event this occurs therapy with penicillin should not be delayed, meanwhile continuing the streptomycin administration.

#### SUMMARY

1. The literature on the various types of infection due to *B. pyocyaneus* is reviewed and ten cases are described in detail, including one case of endocarditis and one of pneumonia.

2. Local infections due to *B. pyocyaneus* are frequent and usually benign. The most common sites are superficial surgical wounds, the skin and the lower urinary tract. The organism is often seen as a secondary invader in chronic otitis media. Corneal ulcers are rare but important because of the tendency when untreated to progress to panophthalmitis.

3. The clinical picture in sepsis due to this organism is summarized from the literature and exemplified by four typical cases. Important features include the high mortality rate, tendency to occur in infants and children and in debilitated adults, and frequent occurrence of ulcerating gangrenous lesions in the skin ("ecthyma

gangrenosum") and throughout the gastrointestinal tract.

4. In treatment the sulfonamides and streptomycin are the agents of choice. Streptomycin appears to be as good as, and in some instances, better than the sulfonamides, particularly in urinary tract infections. Factors which seem to be important in the lack of success of treatment with streptomycin in sepsis are the frequent presence of other serious disease producing general debility and occasional rapid development by the infecting organism of resistance to the chemotherapeutic agent. For local infections applications of 1 to 2 per cent acetic acid have been known to be efficacious for many years. Recently good results have been obtained in such conditions by the use of phenoxetol and of a solution containing 10 per cent urethane and 1 per cent sulfanilamide.

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# Seminars on Rheumatic Fever

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## Clinical and Laboratory Diagnostic Criteria of Rheumatic Fever in Children\*

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IT is the purpose of this seminar to present the clinical manifestations of rheumatic fever as seen in a large group of children six to sixteen years of age. The natural course of the disease in this group of children was uninfluenced by therapy, as no medication was administered to this group. The treatment consisted of bed rest and balanced diet and occasional sedation for pain or restlessness. It is the further aim of this discussion to present and evaluate the laboratory aids currently used in arriving at a diagnosis of rheumatic activity. The emphasis will be placed upon evolving a clinical picture of the disease as we see it at a sanatorium where the course of the disease may be followed closely and in detail.

### PART I. CLINICAL MANIFESTATIONS

A full description of the classical clinical manifestations of rheumatic fever fails to give an adequate picture of the disease. The text book procedure of describing the most striking signs and symptoms of the disease has failed to give due emphasis to the more elusive, yet more important manifestations from the point of view of prognosis. Acute polyarthritis and obvious evidence of valvular disease, for example, occupy more attention in the literature of rheumatic disease than does mild progressive carditis or the poorly recognized visceral manifestations

of the disease. The latter, in our experience, constitute prognostically the more important features of rheumatic fever.

These clinical manifestations may be divided into several categories: (1) those that are an expression of the toxicity of the illness; (2) those that are significant of a disturbance in the supporting and nervous structures of the patient; (3) those that speak for manifest rheumatic disease of the visceral structures.

It is clear, however, that although these three categories are distinct, they overlap from time to time or manifest themselves simultaneously. The dominance of one group of manifestations over another, in our experience, is an expression of the individual patient's adaptation to the disease. In this regard age, sex, social status, geographical location and heredity may play a significant rôle. Some manifestations are more common in early childhood; others in adult life. The same manifestations may express themselves somewhat differently at different age levels or in different localities. The important features of the disease, however, are that it is protracted, universal in its distribution in the organism, self-perpetuating and eventually self-limited. These characteristics are uninfluenced by age, sex, color, et cetera. Joint manifestations, for example, are more common and more refractory to treatment in the adult. Chorea, on the other

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hand, rarely occurs after adolescence. Rheumatic carditis is more often recognizable in the child but on closer examination will be found to exist in the adult as well but perhaps in a more elusive form.

#### A. MANIFESTATIONS WHICH ARE AN EXPRESSION OF THE TOXICITY OF THE DISEASE

1. *Fever.* Low-grade fever in rheumatic patients has always been looked upon as indicative, with high probability, of rheumatic activity. A flat temperature curve is commonly relied upon by most physicians as a sign of the cessation of the active rheumatic process. Experience with rheumatic children shows that "fever alone is a common erroneous basis for a diagnosis of rheumatic fever."<sup>1</sup> Our observations indicate that all cases of acute rheumatic disease show a mild febrile course for the first one to six weeks. Occasionally, a child will continue to have a low-grade temperature for as long as twelve weeks. Actually, only one-fifth of the patients, in our experience, have a low-grade fever after the fifth week. It is of some significance to note that all patients during the febrile period of the disease show obvious signs of active rheumatic disease but the great majority (90 per cent) continue to demonstrate rheumatic activity after the temperature is completely normal. (Fig. 1B.)

It is to be remembered that many children have a normal temperature range of 99° to 100°F. (37.3° to 37.8°C.) It is deplorable to think that many a child has been sent away from home with a diagnosis of rheumatic fever simply on the basis of a low-grade temperature, without any other manifestations. It cannot be emphasized too strongly that fever as a single manifestation of rheumatic disease is an unreliable criterion of rheumatic activity.

2. *Failure to Gain Weight.* For some time, a consistent gain of weight has been

considered indicative of the onset of the quiescent phase of rheumatic fever.<sup>2</sup> Our observations show that more than one-half of the children are either normal in weight or above normal at the beginning of the rheumatic episode. All of these children show a slight loss in weight during the first eight to nine weeks of the active disease but by far the vast majority (85 per cent) begin to gain weight after the ninth week following the onset of active rheumatic disease. In our group of cases, two of every five children continue to show mild rheumatic activity although they had reached a normal weight gain level. (Fig. 1F.) A return to normal weight gain level of the patient cannot, therefore, be used as a criterion for the cessation of rheumatic activity.

3. *Appearance and Behavior of the Patient.* Clinicians have observed for many years that the rheumatic patient presents a typical appearance during the acute phase of the disease. His pallor has been described in various ways and has been considered typical of the acute process. It has been observed that the pallor is far greater than one would expect from the level of hemoglobin. It has further been noted by pediatricians and students of rheumatic disease that the child suffering from rheumatic activity shows a high degree of emotional instability. His appetite is capricious. His sleep is restless. His habits of evacuation and urination are disturbed. Marked and frequent fluctuations of expressions of elation and depression are commonly observed during the active phase of the disease. Easy fatiguability in active rheumatic patients is a common occurrence. The child who under normal circumstances is anxious to participate in childhood activities, during the mild active disease devises ways and means of substituting less vigorous and in some instances completely circumscribed activity, provided he is given a chance to do so.

These clinical manifestations as expressed

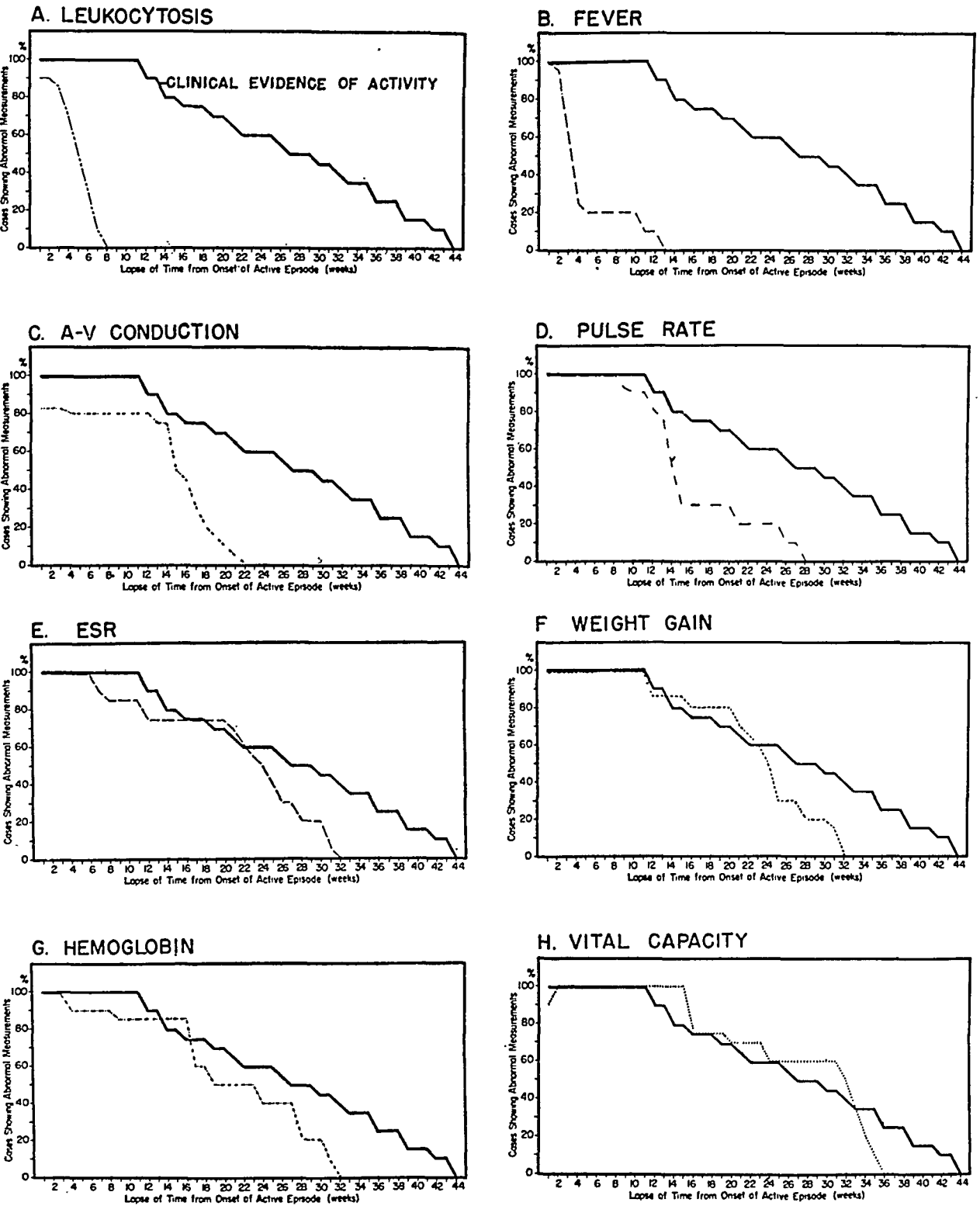


FIG. 1. Per cent of cases showing abnormal laboratory and clinical measurements in relation to lapse of time from the onset of the active episode. (Courtesy of *J. Pediat.*, 29: 77-89, 1946.)

in the appearance and behavior of the patient are indeed very often the only signs of rheumatic activity and, in our experience, may be relied upon as important criteria for the diagnosis of active rheumatic disease.

#### B. MANIFESTATIONS SIGNIFICANT OF DISTURBANCE IN THE SUPPORTING STRUCTURES AND NERVOUS SYSTEM

1. *Joint and Muscle Pain.* In rheumatic children, arthralgia and myalgia, are not often clearly defined. A careful history will reveal that the majority of young rheumatic children complain of muscle and joint pain in the lower extremities. A detailed analysis of these complaints, however, brings into clear relief a distinct classification of these complaints from the point of view of diagnosis. Many rheumatic children complain of joint and muscle pains but these are unrelated to the rheumatic diathesis. In our experience, such complaints occurring at night and relieved by the application of heat are almost always significant of "growing pains" and do not constitute one of the symptoms of rheumatic disease. Similar symptoms occurring during the course of physical activity in a rheumatic child are in most instances significant of rheumatic disease. When such complaints are continuous and uninfluenced by the application of heat or light massage, other clinical and laboratory criteria of rheumatic activity are usually discovered on careful examination. But when these complaints are evanescent and are clearly associated with fluctuations in the weather, other criteria are not found as a rule although there is evidence to show that this type of arthralgia or myalgia is a characteristic complaint in quiescent rheumatic disease.

It is, therefore, of considerable importance to distinguish between growing pains, the joint and muscle pains of the quiescent rheumatic patient, and those associated with

rheumatic activity. In our experience, the latter occur in three of every four patients suffering from rheumatic disease if a careful history is taken.

Migratory polyarthritis has been considered by many as the most common and typical manifestation of rheumatic fever. In children this syndrome is not too impressive. It does not occur as frequently as in the adult. In our experience, rheumatic fever in children is diagnosed more frequently in the absence of polyarthritis. Indeed, when this syndrome occurs it offers considerable difficulty in diagnosis. It is not always clearly separated from rheumatoid arthritis, serum sickness and other allergic joint manifestations. In fact, it is hazardous to make a diagnosis of rheumatic disease in children on the basis of polyarthritis alone. It has been stated by some quarters that migratory polyarthritis which follows a beta hemolytic streptococcal infection or scarlet fever should be considered as of rheumatic origin. Our observations in children do not always concur with this contention. We have not been convinced that when polyarthritis occurs as a single manifestation following a beta hemolytic streptococcal infection, the diagnosis of rheumatic fever is always substantiated. Many such cases do not present other rheumatic manifestations in their follow-up history. We are rather impressed with the finding that rheumatic polyarthritis in children is always associated with other criteria for the diagnosis of rheumatic fever; that the absence of other criteria puts the diagnosis of rheumatic polyarthritis in doubt. Our evidence further shows that all children with definite rheumatic polyarthritis not only present clinical and laboratory evidence of rheumatic disease but few indeed escape obvious cardiac damage. This becomes manifest on careful physical examination. Furthermore, the "rule" that rheumatic polyarthritis is always temporary and reacts favorably to salicylate therapy



cannot be relied upon in making a diagnosis of rheumatic disease. While it is true that most patients can be controlled rapidly and completely by appropriate therapy, those which are not relieved by salicylate therapy and are of long duration may nevertheless be of rheumatic origin. In addition, many cases with toxic and allergic joint manifestations are frequently temporary in nature and are often favorably influenced by salicylate therapy. Our evidence, therefore, would seem to show that emphasis must be placed upon finding other clinical and laboratory criteria of rheumatic activity before a diagnosis of rheumatic polyarthritis can be established.

2. *Skin and Mucous Membranes.* The skin manifestations of rheumatic disease take on various characteristics (erythema annulare, marginatum, and nodosum). Erythema marginatum is considered by most students of rheumatic fever as a typical manifestation. It is always associated with other signs and symptoms of rheumatic disease and most frequently, in our experience, with the visceral type of rheumatic activity. This cutaneous manifestation may be evanescent or lasting; it may be widespread or localized. It is not associated with discomfort or itching. It is always associated with carditis. Similarly, subcutaneous nodules always establish the diagnosis of rheumatic activity. These occur late in the disease and are also always associated with acute carditis. The incidence of nodules in rheumatic patients is proportional to the care with which they are searched for. The larger nodules are clearly defined and usually occur on the bony prominences. These are not missed as often as those that are attached to the tendon sheaths, deep fascia and superficial aponeuroses. Only detailed observation and palpation is rewarded by the finding of these small nodules.

The prognostic significance of subcutaneous nodules and erythema marginatum has

been discussed for many years. In our experience, erythema marginatum occurs in patients who have well advanced rheumatic disease. Rheumatic nodules are always associated with severe and protracted heart disease. In these instances, they have been looked upon as indicative of a poor prognosis. In some quarters, on the other hand, rheumatic nodules are considered an expression of the stage of proliferation or healing; hence, a favorable prognostic sign. Statistical analysis of our clinical material fails to assign a distinct prognostic significance to the occurrence of rheumatic nodules. Some children having numerous and universally distributed crops of nodules recover from an acute rheumatic bout and seem to present a good outlook for the future. Other patients develop subcutaneous nodules in the terminal stage of the disease.

*Epistaxis:* Nose bleeds are common in children suffering from rheumatic disease. Occasional non-traumatic and non-irritating mild epistaxes occur more frequently in rheumatic than in non-rheumatic children, but do not always signify rheumatic activity. Bouts of profuse epistaxis of sudden onset, however, are always associated with active rheumatic carditis in rheumatic children. Cauterization of the nasal mucosa in the first group is always successful in stopping epistaxis; in the second group during the course of active rheumatic disease, cauterization frequently fails to control the bleeding. It must be said that exsanguinating nasal bleeding is not seen as frequently now as described in the older texts on rheumatic disease. The reason for this is not clear. In the course of nine years experience at a sanatorium where hundreds of children have been observed for many months during the course of rheumatic activity, the nasal tray has been used only on rare occasions.

3. *Central Nervous System.* Little has been added to the clinical picture of chorea since the time of Sydenham. This clinical picture,

however, is descriptive only of the explosive phase of chorea and does not clearly define its relationship to the rest of the rheumatic syndrome complex. Our observations seem to show that: (1) Chorea as a rheumatic manifestation begins months in advance of the obvious muscular incoordination. Emotional instability, restlessness, capriciousness, and other less obvious personality changes are always apparent many weeks before actual bizarre choreiform movements begin. In addition, such personality deviations continue in many instances for years following "acute" chorea. (2) Nearly one-half of the cases of chorea are associated with other rheumatic manifestations. While carditis, rheumatic pneumonia, nephritis, hepatitis and other visceral manifestations are not frequently seen in cases whose dominant rheumatic manifestation is chorea, the incidence of valvular disease in so-called "pure" chorea is only slightly lower than in those whose dominant manifestation is polyarthritis. The distinct difference between the two groups is in the duration of the evolution of the valvular disease. Chorea cases must be observed for many years before cardiac damage becomes manifest. (3) Chorea rarely appears in the adult and is therefore of little diagnostic value in rheumatic disease in the adult. It seems to be more common in girls and sometimes recurs during the pregnant state.

#### C. VISCERAL RHEUMATISM

1. *Respiratory System.* The significance of rheumatic bronchitis has not been sufficiently stressed in the medical literature. In our experience, it is prognostically one of the most important manifestations of visceral rheumatism. Children who present signs of bronchitis during the course of rheumatic activity do not do well as a rule. Therapy directed toward the relief of cardiac decompensation or toward the re-

lief of bronchial spasm does not produce the expected results. These cases are always associated with severe carditis and are frequently observed in the terminal stage of the disease. It is of some importance to note that oxygen therapy, which is often a life saving measure in rheumatic carditis in our experience, is contraindicated in the bronchitic type of rheumatic disease. A concentration of as low as 50 per cent oxygen almost immediately produces severe asthma with urgent air hunger, cyanosis, restlessness, profuse perspiration and striking expression of anxiety. In all of these cases it becomes necessary to terminate oxygen therapy at once to avoid a catastrophic outcome.

Rheumatic pleurisy is a much more common finding in children with rheumatic activity than would appear from the medical literature. More than half of the cases of rheumatic pleurisy can be diagnosed only by careful roentgenographic study. Many of these cases present indefinite and bizarre types of pain in the chest frequently considered as being due to pericarditis or to coronary insufficiency. Others have typical pleuritic pain which, however, is evanescent and easily controlled with appropriate doses of salicylates. Still other cases have classical pleuritic signs often missed if examinations are not frequent. Our evidence does not seem to indicate a correlation between rheumatic pleurisy and prognosis.

From time to time the term "pneumonitis" is used to describe pneumonic signs which are spotty and temporary. Consonating râles are heard chiefly at the bases and the infrascapular region; rarely dullness and tubular breath sounds are observed in these cases. These findings may change from day to day and may completely subside in twenty-four to thirty-six hours. They are always associated with carditis and are not related to the advent of congestive failure. X-ray examination of the lungs does not disclose any definite consolidation but often

shows an unsuspected interlobar pleural thickening.

The specificity of rheumatic pneumonia has been debated for many years. The clinical picture in children is that of lobular pneumonia associated with rheumatic carditis. There is a marked increase in respiratory rate. Dullness, crepitant râles and bronchial breath sounds are heard in various and scattered areas of the chest. These signs may appear and disappear from day to day but often persist for longer periods. The dominant clinical picture, in our experience however, is that of carditis and not of pneumonia. There seems to be no correlation between the degree of carditis and the occurrence of pneumonia. It is well to remember that rheumatic pneumonia is not favorably influenced by the use of antibiotics or the newer chemotherapeutic agents. Massive doses of salicylates seem to be of more specific help. Unfortunately, however, salicylate hyperventilation is a common occurrence in rheumatic pneumonia. Great care must be taken, therefore, to differentiate between the tachypnea of pneumonia and the hyperventilation of salicylate intoxication.

2. *Digestive System.* Abdominal pain is a frequent complaint in rheumatic children and if clearly delineated is significant of rheumatic activity. This abdominal colic may vary from occasional slight spasmodic para-umbilical pain to severe pain and tenderness simulating an acute surgical condition of the abdomen. Frequently, the symptom complex is indistinguishable from acute appendicitis and the differential diagnosis becomes difficult or impossible. These cases present not only exquisite tenderness and spasm over McBurney's point, but also distinct tenderness in the appendicular region on rectal examination. It is well to remember, however, that there are rarely concomitant symptoms of acute appendicitis in these children. Constipation, diarrhea,

anorexia, nausea and vomiting are not usually observed in these cases. We found that a moderate dose—20 to 30 gr. (1.2 to 2 Gm.) of sodium salicylate given intravenously often helps in the differential diagnosis in such instances. The "acute abdomen" subsides within a few hours after the salicylate level of the blood is raised.

Abdominal pain in a rheumatic patient is often referred pain from an acute fibrinous pericarditis, perihepatitis or perisplenitis. In these cases, salicylate therapy does not usually produce the expected favorable results. Cardiac fatigue occasionally produces abdominal pain. Finally, the occasional association of abdominal periarteritis nodosa with rheumatic heart disease must be kept in mind in the differential diagnosis of abdominal pain in a rheumatic patient.

Enlargement of the liver associated with vague digestive complaints is a frequent finding in rheumatic activity in children. This is always associated with acute carditis but is not, in our opinion, an expression of heart failure. The liver edge may indeed be palpable as low as the umbilicus but more often is only one or two fingers below the costal margin. The liver edge is soft and slightly tender. The epigastric distress is out of proportion to the enlargement of the liver. Dehydration therapy does not decrease the size of the liver in these cases. The liver edge recedes only when rheumatic activity subsides. Our evidence shows that an enlarged liver in the absence of signs of right heart failure is always significant of protracted rheumatic activity of a high degree of severity and is always associated with acute carditis. The prognosis in these cases is not a favorable one.

3. *Rheumatic Nephritis.* Most of our patients with acute carditis show more than occasional red blood cells in the urine and some an occasional granular cast. These findings are not limited to those with evidence of incipient or definite heart failure.

Detailed and careful urine examinations do not disclose sufficient evidence to make a diagnosis of nephritis. Occasionally, typical urinary findings of acute glomerulonephritis are observed. It is not clear from our observations whether these cases represent a specific rheumatic nephritis or superimposed nephritis of other origin. The clinical course is not unlike that of any acute nephritis. Some cases are associated with moderate hypertension. The majority do not present any sequelae and have not been found to develop chronic nephritis.

In rare instances, a specific nephritic syndrome occurs in rheumatic children, i.e. "renal epistaxis." The patient develops profuse bleeding from the kidney. The hemoglobin and red blood cell count drop rapidly, producing a severe secondary anemia. Thus, in a period of forty-eight hours, the patient's hemoglobin may drop from 12 to 4 Gm. This "renal epistaxis" is most frequently found in rheumatic patients who are subject to bouts of nasal epistaxis. On rare occasions it becomes necessary to administer transfusion. This procedure, and this procedure only, will in some instances stop the severe renal bleeding. Once the bleeding has ceased, the patient makes a rapid and uneventful recovery without evidence of chronic renal disease. Renal epistaxis, in our experience, is always associated with acute rheumatic carditis. It does not present the clinical picture of renal embolization. It is associated with severe reactivation of the rheumatic process rather than with significant alteration in cardiac function and the advent of heart failure.

4. *Acute Rheumatic Heart Disease.* Of greatest importance both from the point of view of diagnosis and of management is acute carditis. While the clinical and pathologic relationship of acute heart disease and rheumatic fever was demonstrated conclusively by Bouillard more than a century ago, the diagnosis and prognosis of

rheumatic heart disease has been based almost entirely until recent years upon the state of the valves. As late as 1924, Cohn and Swift stated that it was not possible to say during the acute stage of rheumatic fever, "whether heart disease is likely to be established."<sup>3</sup> They were of the opinion at that time that only long after the acute episode of rheumatic disease had subsided could the diagnosis of heart disease be made.

In recent years, interest has moved from the study of valvular damage to that of acute heart disease. It has become apparent to most clinicians that carditis is the most frequent, the most insidious, and the most damaging manifestation of rheumatic fever. The signs of valvulitis and obvious pancarditis are easily recognizable and have been so well described in the medical literature that they need no further discussion here. It is the mild case of carditis that is troublesome from the point of view of diagnosis. It is this manifestation of rheumatic disease that needs further description and illustration. In our experience, rheumatic carditis in children is almost synonymous with rheumatic activity since few patients having active rheumatic disease can be declared not to have acute carditis.

Despite the great increase in knowledge of the natural history of rheumatic disease and its cardiac manifestations, no criteria have been forthcoming for the diagnosis of rheumatic carditis, when this manifestation is mild. We are impressed with the fact that children having rheumatic carditis present two sets of manifestations: (1) those concerning the general appearance of the patient, and (2) those describing the disturbance in cardiac function as determined by auscultatory examination and cardiographic study of the electrical sequence of events in the cardiac cycle.

As mentioned above, a child who under normal circumstances is anxious to participate in all childhood activities devises ways

and means for substitution of less vigorous and in some instances completely circumscribed activities during the course of mild active rheumatic carditis. During this phase the child is emotionally unstable. He is restless; his appetite is capricious; he presents mild gastrointestinal upsets. There is also a bizarre reaction to his environment; at times he is overly exuberant and at other times falls into a pronounced depressive state. The child is pale and looks more ill than the physical findings would seem to dictate. Increase in physical activities or emotional disturbance accentuates his appearance of illness. It is of some importance to note that as long as rheumatic carditis continues this typical pallor continues.

For many years, frequent and distinct changes in cardiac sounds and murmurs have been considered significant of mild carditis. We are impressed with the fact that the volume and pitch of the first heart sound varies from day to day and often from beat to beat. Murmurs change in quality, direction and extent of transmission. It would seem that the cardiac dynamics responsible for cardiac sounds and murmurs are in a state of flux in active carditis, and stabilize when the disease becomes quiescent. Most clinicians have recognized that in acute rheumatic fever tachycardia with a tumultuous rhythm is significant of carditis. Some believe that rapid increase in cardiac size, (i.e., cardiac dilatation and hypertrophy), increase in the extent of valvulitis, and rapidly advancing signs of cardiac insufficiency—all these are criteria of rheumatic carditis, and the absence of these manifestations has been considered as reliable evidence that active carditis has subsided.

In the last few years, we have come to consider changes in cardiac rhythm as a more sensitive and dependable sign of active carditis. It has been our observation that the cardiac rhythm in acute carditis simu-

lates an embryocardia, irrespective of the cardiac rate. The usual 1:2 rhythm heard in normal hearts at a slow rate is completely lost in acute carditis and more nearly approaches a 1:1 rhythm. The interval between the first and second heart sounds is equivalent to or longer than that between the second and first. This type of rhythm is not modified by the cardiac rate as long as acute carditis continues.

It is only when active rheumatic disease subsides that this specific disturbance in cardiac rhythm gradually returns to normal. The period during which restoration to the normal 1:2 ratio occurs is of long duration in most cases. Careful auscultatory examination reveals that complete physical and emotional rest in a patient with acute rheumatic disease approaching the quiescent stage may present a normal cardiac rhythm which, however, is easily disturbed when physical and emotional disturbance occurs. The nearer the patient approaches the quiescent state, the less pronounced is this disturbance during physical or emotional exertion. When, however, the usual physical and emotional activities fail to cause a disturbance in the systolic-diastolic sequence of events as described, rheumatic activity in the heart muscle, in our experience, very likely is at an end.

Thus, it has become clear from careful and detailed observations of large groups of children with rheumatic carditis that the unstable character of the cardiac rate, the ever changing heart sounds and murmurs, and the disturbance in relationship of systole to diastole constitute the primary criteria for rheumatic carditis. Our experience has shown that when children who present these criteria, even if all other laboratory signs of rheumatic activity have become normal, are permitted to assume normal physical activities, signs of rheumatic reactivation and progressive cardiac damage are certain to

become manifest within a short period of time. (Table I.)

TABLE I  
EFFECT OF PHYSICAL ACTIVITIES UPON RHEUMATIC CARDITIS

Patients	No. of Patients	No. of Reactions	Percentage Increase in Cardiac Enlargements
Children who received complete bed rest during entire period of rheumatic carditis.	55	2	4
Children who were permitted limited physical activities when all criteria of rheumatic carditis have subsided except a prolongation of the Q-T interval.....	50	26	11

Acute pericarditis as a manifestation of rheumatic heart disease has been described repeatedly and needs no further discussion here. It is significant, however, that careful and repeated examinations of children having acute rheumatic disease will demonstrate the occurrence of fibrinous pericarditis more often than would appear from the literature. Three of every four children with acute rheumatic heart disease exhibit a pericardial friction rub at some time during the course of the disease. It is also of some importance to note that pericarditis with effusion is, in most cases, favorably influenced by massive salicylate therapy. In our experience, thoracentesis is rarely necessary.

#### SUMMARY OF CLINICAL MANIFESTATIONS

It appears, therefore, that rheumatic fever in children expresses itself in various ways depending upon the spread and severity of the rheumatic process. It may affect any part of the body, visceral as well as the supporting structures. From our experience with rheumatic children it would seem clear that from the point of view of both diagnosis

and prognosis, emphasis should be placed upon the visceral manifestations rather than upon joint, skin or central nervous system signs and symptoms. Joint manifestations, skin manifestations and chorea are expressions of short explosive phases of a long-standing disease and do not help in deciding as to when rheumatic activity begins or ends. Careful observation of the patient as a whole and more detailed study of the disturbances of the function of his heart are rewarded by a more accurate diagnosis of rheumatic activity.

The clinical manifestations of rheumatic disease which dominate the scene may differ from patient to patient. This, in our experience, depends in the main upon the age of the patient. We believe, however, that in most instances rheumatic activity very likely continues for the greater portion of the childhood years; that the clinical manifestations which have been described are simply expressions of the explosive phases of the disease; and that so-called subclinical rheumatic activity goes on even in the absence of these clear-cut clinical manifestations. (Fig. 2.)

We have come to consider evidence of disturbance in cardiac function as one of the most important signs of rheumatic activity. Further progress in diagnostic criteria of mild rheumatic carditis would be helpful in arriving at a decision when rheumatic activity begins or finally comes to an end.

#### PART II. LABORATORY CRITERIA OF RHEUMATIC ACTIVITY

In recent years many laboratory tests have been proposed to measure rheumatic activity. It must be admitted that some of these tests have won confidence in the mind of the general practitioner as a means for determining when the disease is no longer active. Clinicians and students of rheumatic fever are aware of the fact that none of these

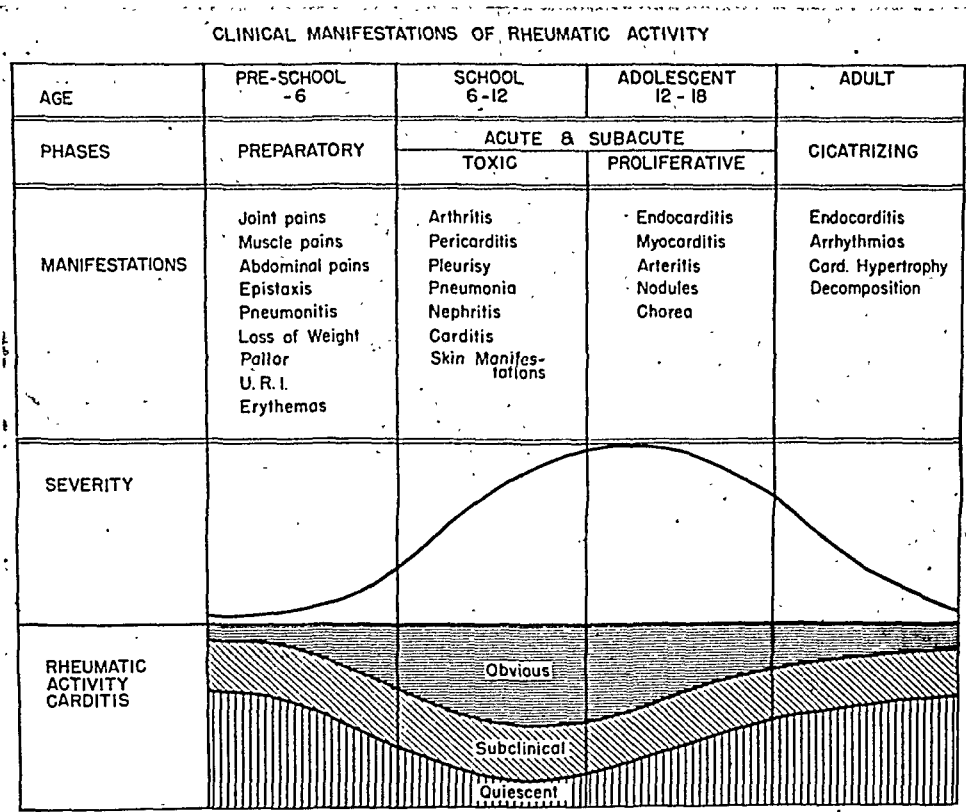


FIG. 2. Schematic representation of the usual clinical rheumatic manifestations and percentage incidence of rheumatic activity in the form of carditis in relation to the age of the patient. "Obvious" represents the usual text book signs and symptoms of carditis. "Subclinical" represents evanescent clinical and electrocardiographic evidence of carditis in the absence of the usual laboratory criteria of rheumatic activity. "Quiescent" represents all other cases that do not show any evidence of rheumatic activity. The curve opposite "Severity" represents the degree of carditis encountered. One plus severity: patients who present laboratory evidence of rheumatic activity and, in addition, present the clinical criteria of cardiac involvement; that is, changing heart sounds and murmurs, labile cardiac rate and fatigability. Two plus severity: patients who, in addition to the foregoing findings, show definite cardiographic evidence of conduction disturbance or/and changes in the ventricular complexes. Three plus severity: patients who, in addition to the foregoing, present a tumultuous heart with moderate symptoms of impaired cardiac reserve. Four plus severity: patients with acute pancarditis.

tests, singly or in combination, can serve as an adequate screening method of rheumatic activity. Yet many are inclined to consider these tests pertinent "in evaluating the presence of active rheumatic fever."<sup>1</sup>

Our experience seems to show that none of the currently used laboratory measurements can be used as specific diagnostic criteria for active rheumatic disease. This conclusion is based upon evaluation of laboratory tests done upon a large group of

rheumatic children who were observed daily from the very onset of the active episode and for many months following obvious rheumatic activity.

LEUKOCYTOSIS

The value of the leukocyte count as an index of rheumatic infection in children has been discussed for more than two decades.<sup>4</sup> Some observers found it helpful in the classification of the degree of rheumatic activity.<sup>5,6</sup>

One in every ten of our cases showed no elevation of the white blood count at any time during the entire course of active rheumatic carditis. Nine of every ten showed a leukocytosis during the first two weeks of the illness, and seven of every ten continued to show such elevation at the end of the fourth week. No leukocytosis was observed in any of our cases after the seventh week after onset of the active episode. All our cases with leukocytosis at the onset showed a definite decline in the total white blood count with lapse of time. It is significant that while all cases with leukocytosis had obvious manifestations of clinical rheumatic activity, nine of every ten cases continued to show clinical evidence of active rheumatic disease after the total white blood count had returned to normal. (Fig. 1A.)

#### PULSE RATE

An increase in the pulse rate out of proportion to the elevation of temperature is a frequent finding in acute rheumatic fever. Thus, children who have a temperature of 101° to 102°F. (38.4° to 38.9°C.) may have an average pulse rate of 140. Similarly, other children whose temperature is normal may continue to have a pulse rate of 120 to 130 when rheumatic activity is present.

In the first three weeks after the onset of illness the pulse rate in our group of cases was found to be higher than at any other time thereafter. None of the patients showed a pulse rate of less than 100 before the end of the ninth week from onset of the acute episode, and none had an elevated pulse rate twenty-seven weeks after the onset. The most marked decline in pulse rate was observed at the beginning of the tenth week.

It is noteworthy that four of ten children whose pulse rates remained normal continued to show clinical evidence of active rheumatic disease. On the other hand, a few cases who were apparently quiescent showed occasional sinus tachycardia. (Fig. 1D.)

#### SEDIMENTATION RATE

It is generally appreciated that an increase in the erythrocyte sedimentation rate is found in most toxic and infectious diseases. In rheumatic disease, an increase in the erythrocyte sedimentation rate has been considered as the most useful finding in evaluating the presence of rheumatic activity, and some observers are inclined to look upon it as of specific diagnostic, as well as prognostic, significance in rheumatic fever.<sup>7-13</sup>

In our group of cases, the sedimentation rate was not as good a guide of rheumatic activity as is commonly reported. Many cases had definite active rheumatic disease with a normal sedimentation rate. No evidence of heart failure was observed in this group. All children showed marked elevation during the first eight weeks from the onset of the illness, the elevation being most marked during the first four weeks. At the end of eight weeks, 15 per cent of the cases had normal sedimentation rates but many of these continued to show evidence of active rheumatic disease. After the twentieth week, an increasing number of children showed a normal sedimentation rate, and at the end of thirty-two weeks, the sedimentation rate became normal in all the cases although 40 per cent of the group still showed some clinical evidence of mild rheumatic activity. (Fig. 1E.) Of equal significance is the fact that at the end of the sixteenth week, a number of children who failed to show clinical evidence of rheumatic activity had a slightly elevated sedimentation rate.

#### HEMOGLOBIN

Secondary anemia is usually present during rheumatic activity, the degree of anemia being related to the severity and duration of the manifestations of the disease. It is considered a characteristic finding during active rheumatic carditis.<sup>14-17</sup>



All our patients showed a moderately severe anemia at the onset of the acute episode. During the first week, the hemoglobin ranged between 7 and 9 Gm. for the entire group. From the end of the first to the end of the fourth week, there was a further depression in the hemoglobin level so that at this time the range was only 7 to 8 Gm. At the end of the fourth week, two of the children showed a hemoglobin of 5 Gm. It was only twelve weeks after the onset of the illness that thirty of the children, or about 15 per cent, showed a hemoglobin of  $12\frac{1}{2}$  Gm. or more. Twenty-four weeks after the onset, half of the children had a normal hemoglobin level. It was only thirty-two weeks after the onset that the hemoglobin of all the children had returned to  $12\frac{1}{2}$  Gm. or more.

It may be said, therefore, that in our group of cases none showed a normal hemoglobin at the beginning of the illness; the lowest hemoglobin level was found in the period from the second to the fifth weeks of illness; and all the children showed a normal hemoglobin eight months after the onset of the illness. In a great many instances, the hemoglobin did not return to normal until the activity had subsided. On the other hand, 40 per cent of the cases showed clinical evidence of rheumatic activity after the hemoglobin had returned to normal. (Fig. 1G.)

#### VITAL CAPACITY

It is generally agreed that a diminishing vital capacity is one of the earliest signs of left ventricular failure. It has been suggested that a low vital capacity in a rheumatic patient is to be considered a good index of rheumatic activity in the heart muscle when all other factors which might influence the vital capacity are excluded.<sup>18,19</sup> Reduction of the vital capacity in a rheumatic patient is looked upon as a measure of left ventricular failure even in the absence of the more

obvious signs and symptoms of cardiac insufficiency.

In our experience, the vital capacity seems to be one of the most sensitive criteria of the progress of active rheumatic disease. All children during the active phase of the disease showed a vital capacity of 40 per cent or more below normal for age and body surface. Children below eight years of age were excluded from this group since the vital capacity reading is unsatisfactory at this age level.

For the first three months of rheumatic activity, none of the children showed a rise in vital capacity. Some began to have a slight increase three months after the onset of activity. The rise was small and the number of cases few. After the first three months, more cases showed a gradual rise in vital capacity, but none reached normal for age and body surface until sixteen weeks following the onset of rheumatic carditis. At this time, one in every four children had a normal vital capacity. The last case which returned to normal vital capacity reading was eight and a half months after the onset. On the other hand, even after this lapse of time one-quarter of the cases still showed mild clinical evidence of rheumatic activity. (Fig. 1H.) Thus, while the vital capacity was the last measurement to return to normal, it failed to be a specific diagnostic measurement, as many of the cases continued to show clinical evidence of active rheumatic disease while having a normal vital capacity. Some few children had a low vital capacity but failed to show clinical evidence of rheumatic active disease on repeated examination.

#### ROENTGENOGRAPHIC CRITERIA

It has been our experience that obvious cardiac enlargement as measured by x-ray and fluoroscopy occurs mainly during the course of active rheumatic disease. Thus, most of our cases irrespective of the degree of

valvular damage were shown to have active rheumatic disease when careful chamber studies were made for evidence of even the slightest increase in cardiac size. On the other hand, many of our cases who could not be convicted on clinical or laboratory evidence as having active rheumatic disease did not demonstrate progressive cardiac enlargement over long periods of time although they presented advanced valvular disease.

#### ELECTROCARDIOGRAPHIC CRITERIA

Much has been written on the subject of cardiographic findings in rheumatic disease. Obviously, no clear-cut findings have been described as specifically diagnostic of rheumatic disease. Histologic evidences of cardiac damage in this disease are universal in their distribution and vary in degree from a minimal inflammatory process to complete disorganization of the heart muscle, its endocardium and conduction system. While the conduction system has been considered particularly vulnerable to rheumatic disease, no cardiographic finding significant of conduction disturbance has been found to be specific for rheumatic disease.

Some electrocardiographic changes become fixed and cannot therefore be used as criteria for active carditis. Most electrocardiographic abnormalities described in the literature demonstrate evidence of temporary ischemia or permanent scar formation of the cardiac muscles. Most studies attempt to correlate electrocardiographic findings with the histopathology known to exist in myocarditis and few of these studies take into clear account the pathologic physiology mirrored in the cardiogram in the acutely inflamed heart muscle.

1. *A-V Conduction.* The finding of prolonged auriculo-ventricular conduction time in a rheumatic patient has come to be regarded as evidence of rheumatic carditis even in the absence of other laboratory or

clinical evidence of rheumatic disease, and many a patient has been thus stigmatized as long as his P-R interval has remained prolonged. On the other hand, a return of the P-R interval to normal is looked upon with confidence as a sign of cessation of rheumatic activity.

A significant number of our cases (17 per cent), did not show any prolongation of the A-V conduction time at any time during the entire course of the active rheumatic process. It is probable that some of these might have shown a prolongation of conduction time had electrocardiograms been taken at more frequent intervals. Ninety-nine per cent of the children who had prolonged auriculo-ventricular conduction time at the onset of the carditis showed a normal conduction time later. However, a large proportion of the cases showed clinical evidence of rheumatic active disease when the auriculo-ventricular conduction time had returned to normal. It is of some significance that two cases gave the impression of cessation of active rheumatic disease although the auriculo-ventricular conduction time was still prolonged. Both of these cases showed the same conduction time two years after cessation of activity. (Fig. 1c.)

2. *Precordial Leads.* The addition of precordial leads has increased the incidence of abnormal cardiographic findings in rheumatic fever. Lead IV was found of clinical value as an aid in recognition of myocardial involvement in rheumatic fever; successive changes in the S-T segment and the T waves were interpreted as showing that the cardiac lesions were not in a quiescent state.

3. *Prolongation of Electrical Systole (Q-T Interval).* The impression gained from careful auscultation of the hearts of children suffering from acute carditis is that there is a distinctive disturbance in the normal sequence of events in the cardiac cycle as regards the length of systole in relation to diastole. In order to test this thesis, we have

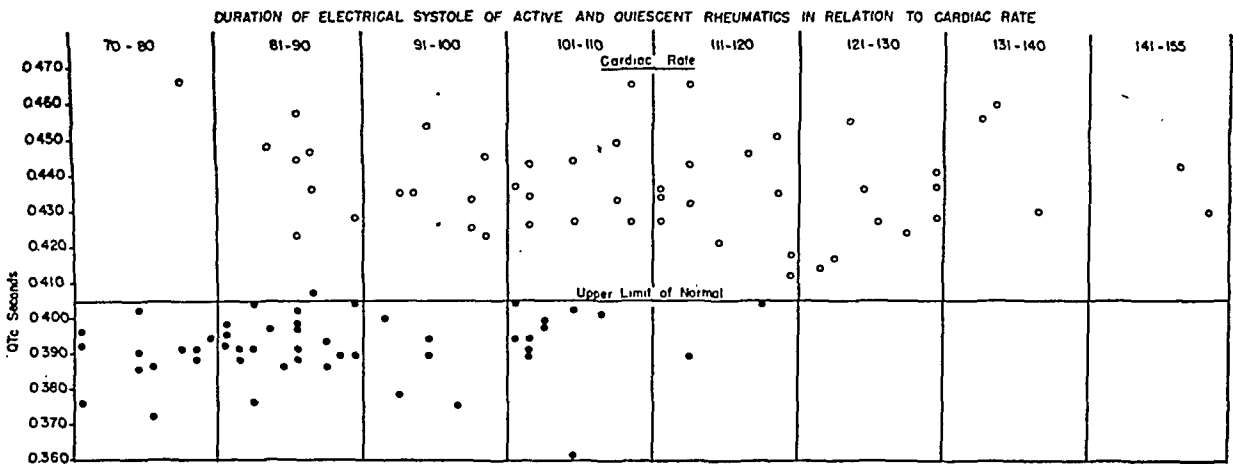


FIG. 3. Duration of electrical systole in children with active and quiescent rheumatic fever in relation to cardiac rate. On this chart, fifty "active" and fifty "inactive" cases are distributed according to the Q-Tc of the patients at the time of the observation and the cardiac rate at the same time. (Courtesy of *Am. Heart J.*, 33: 14-26, 1947.)

for many years measured the electrical systole in children having rheumatic carditis. Since the electrical and mechanical systoles, for clinical purposes, are equivalent, a disturbance in the relationship between systole and diastole would show up in the measurement of the electrical events in the cardiac cycle. Our studies show that:<sup>20</sup>

1. "The duration of the electrical systole (Q-T) both absolute and relative to diastole is significantly prolonged in all cases of acute carditis. (Fig. 3.)
2. "This prolongation does not seem to be a function of cardiac rate in these cases but rather that of the severity of the disease."
3. While it cannot be said that the prolongation of the electrical systole signifies an acute inflammatory process in the heart muscle, our studies show that all cases of acute carditis present such a disturbance in the electrical sequence of events of the cardiac cycle.

For the present we are satisfied with the observation that prolongation of the electrical systole in the cardiograms of children suffering from rheumatic carditis is an important diagnostic criterion of the presence and degree of rheumatic activity in the heart muscle. There is evidence to show that this finding precedes all other laboratory

criteria of rheumatic activity and does not return to normal for long periods of time after all other criteria have reached a normal level.

SUMMARY OF LABORATORY CRITERIA

In summary then, those laboratory and clinical measurements upon which considerable reliance is placed in evaluating the progress of rheumatic disease do not seem to be adequate for a diagnosis of rheumatic activity. At the end of nine months after the onset of rheumatic activity all children in our group showed normal white blood counts, hemoglobin, sedimentation rate, vital capacity and pulse rates. At this time, a large percentage continued clinically to demonstrate rheumatic activity. While it is true that some of the laboratory tests remain abnormal for a longer period of time than others, none of those currently used is adequate in screening all cases of active rheumatic disease. In our experience, a study of the electrical events in the cardiac cycle seems, for the present, to be the most sensitive method of detecting the presence of rheumatic activity.

DISCUSSION

QUESTION: On what basis can we make a diagnosis of rheumatic disease in a patient

who has definite evidence of mitral stenosis but does not present a definite history of rheumatic fever or rheumatic symptoms? The current teaching seems to be that the etiological diagnosis of rheumatic disease cannot be made unless there is a definite history.

DR. TARAN: Mitral stenosis should always be set down as rheumatic in origin unless another etiologic basis is known. It might be said, however, that in our experience no case of mitral stenosis was observed without a history of rheumatic disease. It must be admitted that these histories are often very difficult to obtain.

QUESTION: There are some studies in the literature which seem to postulate that chorea is not a manifestation of rheumatic fever. How do you explain such conclusions?

DR. TARAN: In the light of our present knowledge such conclusions cannot be accepted. In the first place, most cases of chorea have other manifestations of rheumatic disease. In the second place, careful follow-up of chorea patients over long periods of time show an incidence of classical rheumatic heart disease much higher than one would expect in any normal group of individuals.

QUESTION: Not infrequently one sees in private or clinic practice children with a known history of rheumatic disease who present no rheumatic manifestations or symptoms but who have a slight elevation in temperature daily for many weeks or months. No explanation for this fever can be discovered on physical examination. How are we to interpret this low-grade fever?

DR. TARAN: It is common experience that some very active children normally have a temperature above the so-called normal, particularly following vigorous physical activity. A temperature slightly above 100°F. (37.8°C.) is not infrequently registered in this group of children late in the afternoon. A short rest lowers the temperature

level to "normal." In our experience, such individuals are found among rheumatic children with the same frequency as among normal groups of children. It is noteworthy that the daily fluctuation of temperature in this group is not measurably greater than the average for any group of children.

Occasionally, a child recovering from an acute rheumatic episode continues to have a slightly elevated temperature for many weeks while at rest. Our observations seem to show that this isolated clinical finding cannot be considered significant of rheumatic activity. More often than not, such patients show a normal temperature level when they are returned to normal physical activities.

QUESTION: How much reliance can one place upon the finding of a rapid pulse rate in a child?

DR. TARAN: The sleeping pulse rate is a good index of the actual cardiac rate as it excludes the hurried heart rate resulting from the inimical doctor-patient relationship. It should be remembered, however, that many children go through their day's experiences during sleep. This may produce a hurried cardiac rate during sleep. In most children, in our experience, a carefully studied approach to the child will avoid all apprehension and the cardiac rate observed under these circumstances can be relied upon as representing the actual rate.

QUESTION: Not infrequently one sees a child with rheumatic disease who after several weeks of bed rest does no longer present any rheumatic manifestations except an elevated sedimentation rate. Would you allow such a patient to assume normal activities gradually?

DR. TARAN: Yes, if I were reasonably assured that this patient no longer presents clinical evidence of rheumatic activity. In our experience, the elevated sedimentation rate in such a patient is not significant of rheumatic activity. If no other explanation

for the elevated sedimentation rate can be found, the patient should be observed but not stigmatized as having active rheumatic disease on the basis of this finding alone.

QUESTION: You state that the prolongation of the electrical systole (Q-T) is characteristic of acute carditis and is a valuable method for evaluating the severity of carditis. What is the physiologic significance of this finding? Little mention is made of the clinical significance of the Q-T interval in most texts on cardiography. Is there any explanation for this omission?

DR. TARAN: Physiologists have always contended that disturbance in the time relationship of systole and diastole is a manifestation of impairment of the functional integrity of the myocardium. They found consistently that the period of systole was of longer duration in functional cardiac disorders. When more than normal blood returns to the ventricle, it responds by expelling more blood not only by a greater number of ejection periods but also by a greater relative duration of each systole. To the physiologist the duration of systole in a diseased heart as compared with the normal heart gives a method of determining the functional integrity of the myocardium; and some physiologists state that the duration of systole in the abnormal heart is a measure of dilatation.

There is, however, a wide difference of opinion among cardiographers and clinicians regarding the clinical importance of the measurement of the duration of the electrical systole (Q-T). Katz<sup>21</sup> states that "there is little practical value in measuring the duration of electrical systole." Ashman,<sup>22</sup> on the other hand, believes that measurement of the electrical systole may give valuable information regarding the degree to which the myocardium is affected in diphtheria or in acute rheumatic carditis. Cheer<sup>23</sup> presented evidence to show that the electrical systole (Q-T) is greatly increased

in heart failure irrespective of etiology and proposed the concept that an increased electrical systole may indicate a disturbance of cardiodynamics which might well be formed before clinical evidence of failure is available. Drawe<sup>24</sup> and his associates find that the Q-T interval is definitely prolonged in about 25 per cent of the rheumatic children he observed. On the other hand, White and Mudd<sup>25</sup> conclude that the duration of the Q-T interval is apparently of little or no clinical value.

It is clear that while physiologists are in agreement that prolongation of the duration of systole (Q-T) is significant of a disturbance in the functional integrity of the myocardium, clinically insufficient evidence has been forthcoming in support of the physiologic concept. This discordance of opinion may be explained on the basis that the study of the component parts of the cardiac cycle have not been closely investigated in hearts showing acute impairment of myocardial function such as rheumatic carditis but rather in cardiac conditions of long-standing in which functional compensation has already been established at a given level of cardiac reserve.

#### SUMMARY OF SEMINAR

The clinical manifestations and laboratory criteria of rheumatic activity have been the subject for discussion in this seminar. It has been pointed out that rheumatic disease in children is a long-standing systemic disease presenting systemic and localized clinical manifestations. It has also been pointed out that while the number of clinical manifestations are many and varied, the dominant feature of the disease is protracted, long-enduring activity manifested mainly in disturbance in the cardiovascular system. It has further been pointed out that emphasis should be directed toward the diagnosis of *mild* rheumatic activity. More attention is to be given to the patient and

his heart. It is believed that all cases of rheumatic activity demonstrate clinically cardiac auscultatory findings significant of disturbance in the functional integrity of the heart.

It has further been pointed out that all the laboratory tests currently used in the diagnosis of rheumatic activity are inadequate in screening rheumatic activity. The most sensitive criterion for rheumatic activity for the present seems to be a careful study of the cardiac events in the electrocardiogram. Observations seem to show that rheumatic activity continues for long periods of time after temperature, pulse rate, white blood count, sedimentation rate, hemoglobin and vital capacity have returned to normal. The disturbance in the sequence of events in the cardiac cycle, however, is the last criterion to return to normal and, in our experience, seems to coincide as closely as possible with the cessation of rheumatic activity.

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# Combined Staff Clinics

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## The Nephrotic Syndrome

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ROBERT F. LOEB: Dr. Coleman is going to summarize the story of a girl who was in this hospital one year ago and at that time presented the classical picture of the nephrotic syndrome.

DR. THOMAS COLEMAN: This is E. L., now twenty-one. The story of her disease begins three years ago when, in July, 1943, at the age of eighteen, she first began to notice intermittent ankle edema. The edema increased and she consulted a doctor. He found a 4 plus albuminuria. Her weight at that time was 148 pounds. Her doctor put her on a low-salt, low-protein diet, on which she stayed rather regularly for one year. During the last three months of that year she began to lose weight rather markedly, became very pale, had anorexia, severe nausea and vomiting. When she reached the weight of 113 pounds she decided voluntarily to break the diet and began eating anything she liked, including salt. She then gained weight for one year despite treatment with diuretics by a second physician. Her weight had increased to 158 pounds at the time of her first Presbyterian Hospital admission in July, 1945. She had never had any acute upper respiratory or other infection. Characteristic symptoms of acute glomerulonephritis could not be elicited in her history. She had no exposure to nephrotoxins such as carbon tetrachloride. There was no history of hypertension. In short, her past history was noncontributory.

On physical examination at admission she showed massive edema, ascites, bilateral hydrothorax, pallor. The blood pressure was normal. Her thyroid was enlarged. The initial tests showed an antistreptolysin titer of less than 50. The phenolsulfonphthalein excretion was 50 per cent after two hours. The Kline test was negative. Nose and throat culture was negative for hemolytic streptococcus and pneumococcus. The basal metabolic rate was minus 20 per cent. Fasting blood sugar was normal.

Her treatment consisted of diet low in sodium and high in protein. She was given diuretics including urea, mercurials and ammonium chloride. She was placed, for a time, on the Schemm regimen, which is essentially sodium-free but includes a high water intake.

Despite these therapeutic measures she failed to improve. In fact, she gained weight, which was presumably edema fluid. Her weight remained above 160 pounds. Her red blood cell count fell from five million to three million per c. mm.; the hemoglobin from 14 to 12 Gm. per cent; the total serum protein ranged between 3.6 and 2.5 Gm. per cent. Her serum albumin fell on one occasion to as low as 0.8 Gm. per cent. The blood urea nitrogen ranged around 25 mg. per 100 cc., exclusive of a period of urea therapy, at which time it rose. Her cholesterol on admission was 895 mg. per cent, and at one time reached a high of 1,560 mg. per cent; on discharge it was 1,100 mg. per

cent. Her urine during all this time continued to show 4 plus albumin, 2 plus glucose, with many hyaline and granular casts and an occasional red blood cell. After ten weeks without much success in treatment she was discharged to be followed in the out-patient clinic.

She was seen in the clinic at regular intervals for eleven months, during which period

nocturnal muscle cramps and great fatigue. Phenolsulfonphthalein excretion fell to zero. Heavy albuminuria continued, with normal blood pressure. She was then admitted for the second time in October, 1946, for treatment of her anemia.

On admission she weighed 120 pounds and was free of edema. She was given a low-protein, low-sodium diet. She received

TABLE I  
PATIENT E. L., NEPHROTIC SYNDROME

Date	Edema	Albuminuria	Blood Pressure, Mm. Hg.	Hemoglobin, Gm.	Total Serum Protein, Gm. Per Cent	Serum Cholesterol, Mg. Per Cent	Serum N.P.N., Mg. Per Cent	Serum Urea Nitrogen, Mg. Per Cent
June 1943.....	++	+++++						
December 1943.....	0	+++++						
July 1944.....	++	+++++						
July 1945.....	+++	+++++	132/87	14.5	3.6	895		21
August 1945.....	+++++	+++++	135/96	15.4	2.9	1561		54
September 1945.....	+++	+++	128/100	14.0	2.5	1379		29
November 1945.....	++	+++	120/95		4.1	1479	44	
January 1946.....	++	+++++	120/80		6.1	1308	61	
April 1946.....	+	+++++	125/90		3.8	1119	67	
September 1946.....	0	+++++	125/90	4.6	5.4	459	153	
Oct. 5, 1946.....	0	+++++	146/88	4.0	5.5	485		107
Oct. 11, 1946.....	0	+++++		5.0*				62
Oct. 17, 1946.....	0	+++++		6.5†				77
Oct. 23, 1946.....	0	+++++	144/110	7.0‡	5.0	378		97
Nov. 18, 1946.....	0	+++++	190/135	8.0				145
Nov. 22, 1946.....				7.5				170

\* After one transfusion (150 cc. whole blood).

† After two transfusions (450 cc. whole blood).

‡ After four transfusions (1450 cc. whole blood).

she did no work and remained at home. She maintained a rigid salt-poor regimen with a moderate protein intake sufficient to maintain nitrogen balance. The serum albumin rose to 3 Gm. per cent, the serum cholesterol fell from 1,400 to 460 mg. per cent. She lost weight, dropping from 148 to 125 pounds in six months. However, toward the end of her clinical follow-up, the serum non-protein nitrogen began to rise, increasing from 44 to 155 mg. per cent. The hemoglobin fell from 12 to 5 Gm. with a corresponding decrease in red cells. Her appetite was poor. She began to have

1,400 cc. of whole blood and her hemoglobin rose to 8 Gm., the red blood cell count to four million. Despite fluid therapy, her blood urea nitrogen increased during this admission to 130 mg. per cent. Recently, she has shown the first rise in blood pressure, which in the last two weeks has been ranging about 140 to 160 systolic and 110 to 120 diastolic. Her albuminuria continues 4 plus, with casts. She is being discharged today showing marked subjective improvement despite progressive renal failure. The only objective change for the better has been an increase in hemoglobin following



repeated transfusions. The laboratory data on this patient are summarized in Table I.

DR. LOEB: What has transpired in this girl is compatible with the natural history of the nephrotic syndrome and probably bears little relationship to the therapeutic measures employed.

I think perhaps it would be just as well to begin our discussion with the origin of the term "nephrosis," which was coined in 1905 by Friedrich Müller. He applied this name to *degenerative* lesions of the kidney primarily involving the tubules, and used it to differentiate these lesions from *inflammatory* lesions of the kidney. We are concerned today with what has come to be known as the "nephrotic syndrome" and not with all states characterized by tubular degeneration.

As all of you know, the nephrotic syndrome is characterized by heavy albuminuria, edema, hypoalbuminemia, in most instances hypercholesterolemia, and in some instances a lowering of the basal metabolic rate. The nephrotic syndrome is encountered characteristically and most frequently in chronic glomerulonephritis. It is also seen, as you know, in the so-called true or lipid nephrosis. It has been described recently by McCann in *Leptospira* infection. As suspected for a long time, it may occur in secondary syphilis; dramatic cures with penicillin have definitely established this etiology in a few cases. The nephrotic syndrome is encountered also in the so-called Kimmelstiel-Wilson syndrome. It is also seen in amyloidosis and, of course, at times following poisoning with certain chemical agents, notably carbon tetrachloride. So you see the development of the nephrotic syndrome is not limited to purely degenerative disease of the kidneys, as indicated by Müller originally, but it is associated with both inflammatory and degenerative disorders.

The problem of the relationship of tubu-

lar degenerative lesions to the nephrotic syndrome is both of interest and importance. It should be pointed out in the first place that there are many patients who show marked degenerative lesions in the tubules who do not manifest the nephrotic syndrome. Next, I think it is important to remember that a certain amount of protein traverses the glomerular membrane normally and this is mostly reabsorbed by the tubule cells. It would be generally conceded today that, in the nephrotic state, proteinuria results from glomerular rather than tubular changes. Serum protein appears in the glomerular filtrate either as a result of increased porosity of the glomerular capillaries or because of some change in the electrostatic charges of the capillary membrane. Possibly changes in charges of the protein aggregates themselves may play a part; this is purely speculative.

Another point important to remember is that the tubular lesions which develop in the nephrotic state are probably in many instances secondary to the albuminuria, and are not primary as was originally believed. The evidence for that is three-fold. First, we know that biopsy of a kidney in a patient who has recently developed the nephrotic syndrome may show no histological deviation from the normal structure of the tubular epithelium, whereas later biopsy of the same kidney reveals the typical tubular changes. Second, Gérard in classical experiments on the salamander found that injection of plasma into the peritoneal cavity was associated with development of tubular degeneration in those nephrons connected with the nephrostomes in the peritoneal cavity, whereas the remaining tubules were normal. Finally, Smetana, here at Columbia, extended Gérard's observations and demonstrated graphically that albumin was reabsorbed in large amounts from the tubules with peritoneal nephrostomes when a red azo-protein was

injected intraperitoneally in the salamander. The cells of the tubules communicating with the nephrostomes were loaded with this pink material whereas none of the other tubules contained the protein dye.

As far as the *mechanism of the nephrotic syndrome* is concerned, I think the historical background is of some interest. In 1916 and 1917, Epstein first pointed out what seemed a logical thesis for the mechanism of the nephrotic syndrome. Epstein indicated that with the heavy albuminuria which is present in these patients there is continued loss of serum albumin and some globulin through the kidneys. This in turn he believed gives rise to hypoalbuminemia. Epstein was the first to apply the Starling hypothesis to the formation of edema. He pointed out that if a large amount of serum albumin is lost, the most important osmotic component of the blood is reduced and consequently the development of massive interstitial edema might be anticipated. Epstein further reasoned that if a large amount of serum albumin is lost through the kidneys, the conventional treatment of nephritis by protein starvation was illogical and he suggested that an increased protein intake might restore the serum albumin to its normal level. Experience of the last thirty years has demonstrated that this thesis is not wholly valid. It is general experience that when patients with the nephrotic syndrome are fed massive amounts of protein, positive nitrogen balance may be established and body protein stored; but evidence that a significant increase in serum albumin level is brought about by this treatment is wanting. We now think that the metabolic disturbances in the nephrotic syndrome are probably much more widespread and profound than was appreciated earlier, and that simple leakage of albumin through the kidneys is not alone an adequate explanation for the abnormalities encountered. It has been suggested by

Kendall, Grabfield, Luetscher and others that there appear to be qualitative as well as quantitative changes in the serum protein in the nephrotic state. I am going to ask Dr. Kendall, who has done important work in this field, to talk about his studies on serum proteins in the nephrotic state.

DR. FORREST E. KENDALL: Dr. Loeb asked me to spend about five minutes in telling you what I know about serum proteins in nephrosis. I will not try to discuss any of the technics which have been used in the study of serum proteins. There are many. They include the salt precipitation methods, as exemplified by the Howe procedure; precipitation with alcohol or other organic solvents under controlled conditions, as exemplified by the work of Cohn and his associates; electrophoresis, ultracentrifugal studies, amino acid analyses, quantitative precipitin studies and many more. These investigations all show that blood serum contains an extremely complicated mixture of proteins varying in molecular weight from around 70,000 to several millions. It contains proteins which would be classified as simple proteins and proteins which are associated with carbohydrates and with lipids.

During the past year in this room, in response to a direct question, Dr. Pedersen of Upsala said that he would hesitate to place any upper limit on the number of protein components in normal human serum. But he felt sure that the number would exceed twenty. In view of this, it is apparent that no technic at present available and no combination of technics will give a complete picture of the serum proteins, even in healthy individuals. But we should not allow this fact to make us disregard the value of serum protein studies in connection with disease. It should simply make us more confident that these studies will become increasingly valuable as our knowledge of the serum proteins increases.

It is interesting that from a clinical standpoint the crudest and simplest of the methods for the study of serum proteins is the most important. That is the Howe fractionation procedure, which really tells us very little of the actual chemistry of serum proteins. However, a large amount of data has been accumulated using this technic and it is possible to make certain correlations between the results of the Howe fractionation and some clinical disorders. From a practical standpoint, the Howe method is today and will probably continue for a long time to be the most valuable tool in this field.

Inasmuch as nephrosis, as defined by Dr. Loeb, is characterized by hypoalbuminemia, we will certainly have to say that the level of serum albumin as determined by the Howe method decreases in the nephrotic syndrome, sometimes to extreme degrees. The serum globulins as determined by the Howe procedure usually remain within normal limits. In my experience, serum globulin levels in nephrosis were below those found normally only in patients in whom there was evidence of blood dilution in addition to nephrosis.

The protein excreted in the urine is largely albumin. I place little reliance upon the results of Howe fractionations as applied to the proteins of urine.

What additional information has been obtained by the use of other technics in this condition? As you know, it can be shown by the use of the Tiselius electrophoresis technic that the normal serum proteins can be separated on the basis of their electrical mobilities into four fractions. The fastest moving fraction has been identified as serum albumin. The other three fractions are considered to be globulins, designated alpha, beta and gamma globulins in the order of decreasing mobility and are found in approximately equal amounts in normal serum. If electrophoretic

studies are made upon the albumin fraction obtained in the Howe procedure, it can be shown that it contains some globulin; therefore, values obtained for serum albumin in normal individuals are somewhat lower than those given by the Howe method.

Refinements of technic have shown that these different electrophoretic fractions can be further subdivided. Thus the albumin fraction, when measured at a pH below 4, can be split into two components with approximately two-thirds of the albumin moving in the faster fraction.

In nephrosis or in the nephrotic syndrome, electrophoretic studies show even greater decreases in the albumin level than are found by the Howe technic. Most of the decrease in the albumin occurs in the faster moving fraction. In the globulins, there is usually an increase in alpha globulin and a corresponding decrease in gamma globulin. Table II, taken from a paper by Thorn and his co-workers, shows the distribution of components in electrophoretic schlieren diagrams (pH 8.6 with sodium diethylbarbiturate as buffer) of plasma proteins in the nephrotic syndrome. In patients with the nephrotic syndrome, quantitative measurements are complicated by the presence of large amounts of lipid moving with the alpha and beta components. Estimations of these fractions are subject to very large positive errors due to the high refractive index of the lipid components.

The protein in the urine is largely albumin and most of this albumin is the faster moving fraction. A large part of the globulin in the urine is gamma globulin.

Immunological studies show very much the same picture. By this technic it can be shown that there are at least five distinct globulins and two albumins in normal serum. It can be shown that approximately two-thirds of the albumin is the carbohydrate-free albumin which can be crystallized. I cannot state that this is the albumin

fraction which moves at a faster rate in the electrophoretic cell. I can say that most of the albumin that is excreted in the urine is the crystalline albumin. The serum globulins show the same shift from gamma globulin to alpha globulin which is indicated by electrophoretic technics.

In conclusion, I should say that the characteristic changes in the nephrotic syndrome are decreases in the blood level of those serum proteins which are excreted

seems to me that it is more probable that the results are due to changes in the relative proportions of normally occurring albumins and alpha globulins in the fractions than to the appearance of new proteins.

DR. LOEB: In addition to the changes which occur in the serum proteins in the nephrotic state, edema, as we have said already, is a characteristic feature of this disorder. Edema fluid is essentially a solution of sodium chloride and sodium bi-

TABLE II\*

DISTRIBUTION OF COMPONENTS IN ELECTROPHORETIC SCHLIEREN DIAGRAMS† OF PLASMA PROTEINS IN THE NEPHROTIC SYNDROME

Patient	Albumins	$\alpha_1$ Globulins	$\alpha_2$ Globulins	$\beta$ Globulins	Fibrinogen	$\gamma$ Globulins
	(Per Cent)		(Per Cent)		(Per Cent)	
J. G. ....	7	4	42	28	16	3
L. I. ....	17	5	36	22	16	4
W. H. ....	17	5	21	38	15	4
D. S. ....	26	8	22	30	9	5
K. N. ....	37	6	15	22	12	8
E. B. ....	46	4	34‡		13	3
R. S. ....	32	5		23	(clotted)	20
Normal pooled human plasma	55	5	9	13	7	11

\* Adapted from G. W. Thorn, S. H. Armstrong, Jr., V. D. Davenport, L. M. Woodruff and F. H. Tyler. *J. Clin. Investigation*, 24: 802, 1945.

† Sodium diethylbarbiturate buffer, pH 8.6.

‡ Not resolved.

in the urine, plus an increase in the alpha globulin fraction.

DOCTOR: Is there any evidence that abnormal proteins occur in the serum of patients with the nephrotic syndrome?

DR. KENDALL: I know of no conclusive evidence that nephrotic serum contains proteins not present in the serum of normal individuals. Various investigators have shown that the albumin and globulin fractions of nephrotic serum may differ from corresponding fractions prepared from normal serum in their amino acid content, in osmotic pressure and in their reaction with antisera. However, one must remember that this work was done upon fractions of serum rather than upon pure proteins. It

carbonate with variable amounts of protein. It was shown originally by Blum and simultaneously by Magnus-Levy that if sodium salts such as chloride or bicarbonate are administered to patients with the nephrotic syndrome, there is an increase in water retention. This increase is found in the interstitial fluid; the plasma volume in patients with the nephrotic state is in reality lower than in normal individuals. Furthermore, Blum and Magnus-Levy showed that it is the sodium ion (and not the chloride and bicarbonate ions) which is active in the production of edema because the administration of potassium, ammonium or calcium chloride tends to have a diuretic effect and to decrease water retention. In

view of these differences in specific ion effect on water retention and excretion, the mechanism of renal control of electrolyte equilibrium is, in addition to the osmotic factor, of unquestionable significance in edema production.

Dr. Taggart will discuss briefly sodium and water metabolism in relation to the kidney in the nephrotic syndrome.

DR. JOHN V. TAGGART: Since the clinical problems posed by the nephrotic patient arise primarily from disturbances of salt and water balance, it is fitting that we consider briefly the mechanisms which may be involved in the formation of edema in nephrosis.

The low protein concentration of edema fluid in nephrosis speaks against increased capillary permeability as an important factor. The various diffusible ions are distributed between the plasma and edema fluid in accordance with the Donnan equilibrium. It has been clearly demonstrated that serum and edema fluid obtained from a nephrotic individual retain their original ionic constitutions when separated by a simple collodion membrane. In short, the edema fluid of nephrosis may be regarded as an ultrafiltrate of plasma subject to the ionic balance imposed by the non-diffusible plasma proteins.

It has long been recognized that the scanty urine excreted during the accumulation of edema contains unusually small amounts of salt. Widal, Javal and other investigators at the turn of the century were much impressed by the systematic variations in the amount of edema which could be induced by varying the salt intake in their patients. Such observations led to the belief that the accumulation of edema reflects a specific renal defect in the excretion of sodium chloride. An obligatory retention of water occurs in order that the all-important osmotic equilibria may be maintained.

In recent years plasma clearance studies with inulin, diodrast and *p*-aminohippuric acid have made possible the description of certain discrete renal processes in health and disease. The nephrotic syndrome in chronic glomerulonephritis occurs in the presence of a renal lesion which usually disturbs the normal relationship between the glomerular filtration rate and the functioning tubular mass. Characteristically there is a preponderant diminution of the glomerular filtration rate in glomerulonephritis. This finding suggests that sodium retention may be the consequence of an imbalance between the capacity of the kidney to filter and reabsorb sodium ions. It should be remembered that the total amounts of sodium and water filtered and reabsorbed daily by the normal kidneys are approximately 500 Gm. and 180 liters, respectively, and that relatively minor disturbances of the normal balance could readily account for the sodium and water retention occurring in nephrosis. The functional pattern in so-called true lipoid nephrosis appears to be different from that of glomerulonephritis. Limited observations indicate that the glomerular filtration rate, effective renal plasma flow and functioning tubular mass all tend to have supernormal values. The large kidney of lipoid nephrosis is a large, functioning kidney. This situation, however, does not exclude the possibility of internal imbalances between glomerular filtration and tubular reabsorption.

While the functioning tubular mass, as measured by diodrast or *p*-aminohippuric acid, may give some indication of the activity of the tubular transfer mechanism for sodium, one can say little at this time concerning the nature of the sodium reabsorptive mechanism. Not until such information is available will one be able to assign to the kidney its proper rôle in the formation of edema in nephrosis.

The development of the Starling concept shifted emphasis from a specific renal defect to the rôle of hypoproteinemia in edema formation. The balance between the colloid osmotic pressure of plasma and the hydrostatic pressures in the arterial and venous limbs of the capillaries might well be expected to be disturbed by the lowering of plasma albumin characteristic of nephrosis. The development of this concept in relation to nephrosis was advanced most notably by the studies of Epstein and Leiter. Epstein examined the relationship between plasma protein concentrations and edema formation in nephrotic patients, while Leiter's studies were concerned with the induction of hypoproteinemia by repeated plasmapheresis in dogs. It was their conclusion that the lowering of plasma protein concentrations below certain critical values was almost invariably associated with edema collection and that hypoproteinemia alone offers an adequate mechanism for edema formation. However, in subsequent years there have been all too numerous instances in which investigators have observed the mobilization and excretion of edema fluid without demonstrable changes either in the plasma protein concentration or the colloid osmotic pressure. Thus, hypoproteinemia alone does not appear to offer an adequate basis for explaining the formation and maintenance of edema in nephrosis.

Let us return then to considerations of a specific renal defect in the handling of sodium ions. Loeb, Atchley and their co-workers examined the water and electrolyte balance in nephrotic and normal individuals following the administration of sodium chloride and various other electrolytes. While the responses obtained in the two groups of subjects were qualitatively similar, there were quantitative differences which these investigators considered to be of importance.

DR. LOEB: As Dr. Taggart has pointed

out to you, there is another serious defect in the simple hypothesis of Epstein concerning the mechanism of the nephrotic state, namely, that many patients may achieve complete diuresis spontaneously without any rise whatsoever in the serum albumin level. Spontaneous and complete diuresis may be effected despite levels of only about 1.5 Gm. of serum albumin per 100 cc. This fact suggests that nephrotic edema is not solely a consequence of hypoalbuminemia, although the importance of depression of the serum osmotic pressure should not be minimized, as indicated by the studies of Govaerts and others.

Dr. Peters and also Dr. Van Slyke established what they termed a "critical level" of serum albumin for fluid retention in the body. I think, however, that Dr. Taggart's comments emphasize the fact that these so-called "critical levels" for edema formation are not inviolate. Furthermore, as pointed out by Govaerts, patients with famine edema and marked decrease in serum osmotic pressure have a large diuresis when they assume the horizontal position, i.e., when the hydrostatic pressure is lowered. In the nephrotic patient with even more generalized edema and low serum osmotic pressure, diuresis is not similarly effected by bed rest.

Another indication that mechanisms other than the osmotic factor may be involved in excessive salt and water retention is suggested by the effects of certain steroids, notably desoxycorticosterone. With low serum albumin levels the latter steroid may cause extraordinary increases in the interstitial fluid compartment and massive anasarca may result. At the present time, we ascribe this increased reabsorption of water and of sodium ion to the effect of the steroid upon specific tubular function. Other steroids such as testosterone and some of the estrogens may cause salt and water

retention but to a lesser degree than does desoxycorticosterone.

Another factor possibly involved in the production of the nephrotic state as characterized by massive edema may be the excessive elaboration or decreased degradation of antidiuretic substances. I have asked Dr. Gilman, who I think was the first to demonstrate the presence of antidiuretic substances in the urine of normal but dehydrated rats, to talk about the possible rôle of antidiuretic substances in the development of the nephrotic state.

DR. ALFRED GILMAN: During recent years attention has been focused on derangements in mechanisms of water excretion to account for the accumulation of edema fluid observed during certain clinical syndromes. Many of the observations are pertinent to the present discussion. I would, therefore, like to review very briefly the physiological mechanism of water excretion.

If large amounts of water are ingested, a copious urine flow results. The urine has a very low specific gravity and is practically devoid of electrolyte. This is accomplished by tubular renal mechanisms whereby the reabsorption of water is depressed whereas that of electrolyte is practically complete. This is a rather intricate function which involves osmotic work on the part of the kidney for it should be recalled that the expenditure of energy in the elaboration of a hypotonic urine is just as great as in the elaboration of a hypertonic urine. Thus it is rather paradoxical to find that the ability of the kidney to excrete a hypotonic urine depends not on the presence but rather on the absence of a particular hormone, namely, the antidiuretic hormone of the posterior pituitary gland.

Our present concept of the mechanism by which the renal excretion of water is accomplished is as follows: The degree of cellular hydration is interpreted by sensitive centers in the hypothalamus. These have a

direct connection by means of the hypothalamic pituitary tract with the secreting cells of the posterior pituitary. Dehydration increases the secretory activity of the posterior pituitary; hydration decreases secretory activity. With secretory activity stopped, the circulating antidiuretic hormone is rapidly destroyed and water diuresis results. A finding pertinent to our discussion is the fact that small amounts of antidiuretic hormone escape into the urine and apparently reflect the blood concentration. Thus in hydrated experimental animals and humans no antidiuretic hormone can be detected in the urine, whereas in dehydrated subjects in whom the need for water conservation is great, the urine contains a huge concentration of an antidiuretic substance.

That derangements should occur in such a sensitive system is not at all surprising. The disturbances in water metabolism which accompany posterior pituitary insufficiency are well known in connection with the large daily urine volumes which are characteristic of diabetes insipidus. The possibility that there may be an antithetical syndrome has been largely ignored. Theoretically an abnormally high concentration of antidiuretic substance in the blood could result from (1) an excessive secretion of the posterior pituitary, (2) a failure of the mechanism whereby the antidiuretic substance in the circulation is destroyed in order to permit the excretion of water, or (3) the formation in some other tissue of an antidiuretic substance. In the event that excessive amounts of water are reabsorbed by the kidney, the subsequent reabsorption of electrolyte for the purpose of maintaining osmotic homeostasis would be in order. The result would be a plethora of extracellular fluid.

The possibility that the accumulation of extracellular fluid may be the result of inadequate renal excretion of water has been investigated in three types of disorders;

the ascites of hepatic cirrhosis, the edema of eclampsia and the edema of nephrosis.

Ralli and her associates could find no casual relationship between the formation of ascitic fluid and the concentration of plasma protein in patients with hepatic cirrhosis. However, those patients who were forming ascitic fluid rapidly exhibited a high concentration of an antidiuretic substance in the urine. Conversely, no antidiuretic substance could be detected in the urine of those patients in whom ascitic fluid was not accumulating. They suggest among other possible explanations that hepatic cirrhosis may interfere with the normal destruction of antidiuretic hormone.

A number of investigators have tested the urine of eclamptic individuals for antidiuretic substances. All observations are in essential agreement and I will only cite those of Ham and Landis. They observed that the urine of eclamptics contained significant amounts of an antidiuretic substance which could not be detected in the urine of women experiencing a normal pregnancy. Differences in the characteristics of the antidiuretic substance obtained from the urine and that obtained from pituitary gland prompted Ham and Landis to examine the placentas. They found an antidiuretic substance in the placentas of eclamptic patients in contrast to those obtained from individuals at the termination of an uncomplicated pregnancy.

Finally, Robinson and Farr have examined the urine of nephrotic individuals. In the same patients the urine contained an antidiuretic substance during periods of formation of edema fluid but not during periods of mobilization of edema fluid. They could make no correlation, however, with the direction of fluid movement and the concentration of plasma protein.

This briefly is the status of the possible rôle of antidiuretic substances in the etiology of edema. Obviously the burden of

proof rests with those who champion such a mechanism. However, provocative evidence is already at hand to suggest a primary rôle of the kidney in edema formation.

DR. HENRY ARANOW, JR.: As I remember, Ham and Landis differentiated between their placental antidiuretic substance and the posterior pituitary antidiuretic substance on the basis of chloride excretion. Is this difference in chloride excretion also found in the dry and wet stages of the nephrotic syndrome?

DR. GILMAN: There is a difference of opinion as to the effect of the posterior pituitary hormone on the excretion of chloride. Peters is of the opinion that it has very little effect on the excretion of electrolyte.

Robinson and Farr made no attempt to characterize their antidiuretic substance. They just accepted the fact that it was antidiuretic. As I recall, no studies were made of chloride excretion in their patients. Ralli and her group tried to characterize the substance they found in their cirrhotic patients and as far as they could tell on the basis of chloride excretion, it was identical with the posterior pituitary antidiuretic substance in that it had no effect on the urinary excretion of chloride. Also, they could easily eliminate the effect on chloride excretion of the posterior pituitary by dialysis.

DOCTOR: Since the plasma proteins tend to be low in the nephrotic syndrome, I was wondering whether this acts as a stimulus to production of antidiuretic hormone.

DR. GILMAN: I do not think anyone has made the implication that the production of antidiuretic hormone is necessarily increased in the nephrotic syndrome. We may merely have an altered balance between destruction and production.

STUDENT: If water retention is the result of increased level of antidiuretic substance,



why should just limitation of the sodium intake affect the amount of edema fluid?

DR. LOEB: I would say there that restriction of sodium is not nearly as dramatic as the administration of sodium in the opposite direction.

DR. DAVID SEEGAL: I should like to ask Dr. Gilman if Landis and Ham's work has been confirmed?

DR. GILMAN: There have been four or five studies on the excretion of antidiuretic substances during eclampsia. The authors have tried to relate increased concentrations of posterior pituitary substance to hypertension and edema. There appears to be some relation to edema but not to hypertension. In this respect the observations of Ham and Landis are in agreement with others. However, I do not believe anyone else has attempted to confirm the placental origin of the antidiuretic substance.

DR. LOEB: As additional evidence of a further widespread disturbance in the nephrotic state, I think we can re-emphasize the fact that serum albumin does not increase with high protein feeding as it does in nutritional edema following the administration of a high protein diet. Indeed, it is believed by many that there is a failure of the normal elaboration of serum albumin in these patients. Furthermore, as already pointed out, hypercholesterolemia is a typical finding in patients with the nephrotic state; the reason for this abnormality has not been clarified. Also, as we have said, nephrotic patients very often have a sharp depression of the basal metabolic rate, which cannot be correlated with any demonstrable change in the thyroid gland, and the reason for which is obscure. It cannot be stated at this time whether these changes in the nephrotic state are primary or secondary to the prolonged hypoalbuminemia. I think we can end the discussion concerning possible factors relating to the mechanism of the disease at this point

and turn our attention to the more clinical aspects of the syndrome.

It must be stated at the outset that the *course and duration* of the nephrotic syndrome are to a great extent dependent upon the precipitating cause. Thus, syphilitic nephrosis is terminated promptly by the administration of penicillin. The carbon tetrachloride nephroses end either favorably or unfavorably in a short period of time. The course of "true" or "lipoid" nephrosis and of the nephrotic state of glomerulonephritis is extraordinarily variable and unpredictable.

Patients with the nephrotic stage of chronic glomerulonephritis complain only of the mechanical discomfort resulting from massive edema and perhaps of some fatigue. On the disappearance of edema, the nephritic patient is usually elated and feels at long last that all is well. Unfortunately, in the majority of instances, the loss of edema presages advance of the disease, as illustrated by the girl you saw today. She is cheerful and immensely pleased that she has finally, after three years, lost her edema. With the disappearance of her edema, as Dr. Coleman has indicated, her serum albumin has risen. Her serum cholesterol has fallen. On the other hand, her phenolsulfonphthalein excretion has fallen to zero and she has become profoundly anemic. Her urea nitrogen has now reached levels which suggest that she has but little time ahead.

Happily, there is another course open to at least some of these individuals who revert from their nephrotic phase to a latent phase of glomerulonephritis as characterized by the presence of albuminuria alone. In (Table III) you may see a summary of the course of another patient, who six years ago presented the full-blown nephrotic picture. As you see, in 1946 his serum protein is perfectly normal. He has no nitrogen retention, he has not developed anemia, his

phenolsulfonphthalein excretion is normal, and he has no edema. He has, of course, persistent albuminuria. The only significant change that has transpired in this patient in the course of some six years is that he has developed very definite arterial hypertension. I am going to ask Dr. Seegal to discuss further the question of the course of the nephrotic phase of chronic nephritis.

Next in importance is the question of salt. As you have heard repeatedly, the sodium ion is the sinner in the production of edema, and it is logical to restrict sodium administration in the nephrotic patient. If the sodium ion is adequately restricted, preferably to less than half a Gm. per day, the patient may drink water freely because he will not, in the absence of isosthenuria,

TABLE III  
PATIENT J. A., NEPHROTIC SYNDROME

Date	Edema	Albumin- uria	Blood Pressure, Mm. Hg.	Hemo- globin, Gm.	Total Serum Protein, Gm. Per Cent	Serum Cholesterol, Mg. Per Cent	Serum N.P.N., Mg. Per Cent
1939-1940 incl. ....	+ to 0	0					
January 1941. ....	++	++++	135/95	17.0	4.5	440	140
February 1941. ....	+	++++	137/90	14.0	3.3	535	50
March 1941. ....	++	++++	140/100	17.0	2.2*	585	53*
April 1941. ....	+++	++++		11.0	2.8	704	
December 1941. ....	0	++++		14.0	5.8	423	
January 1942. ....	0	+++	150/100	16.0	6.1	266	30
January 1943. ....	0	++++	135/95	16.0	6.3	281	26
April 1944. ....	0	+++	158/120	17.0	6.4	191	34
April 1945. ....	0	+++	145/110	17.0	7.1	281	31
April 1946. ....	0	+++		17.1	6.0	265	30
October 1946. ....	0	++++	180/150		6.0		30

\* After acacia.

Before that I should like to review briefly the problem of therapy. You know and I know in medicine, by and large, the greater the number of "cures" the less specific is the "cure." In the nephrotic state we have innumerable measures recommended for treatment, and this may be construed as indicating that none of these methods is wholly satisfactory.

Diet is the first to be considered, and as I have said, the results of forced protein feeding have been disappointing. Beyond giving the patient enough protein to maintain nitrogen balance and to restore body protein lost, I think there is little to be said in favor of excessive (3 or more Gm. per Kg.) protein feeding and it is possible that it may increase renal damage, as suggested by Addis.

elaborate interstitial fluid which is very hypotonic. The maintenance of an essentially normal osmotic pressure is a physiological characteristic jealously guarded by the body.

The use of diuretics is, of course, of interest. There are several categories of these agents. I have already mentioned potassium, ammonium and calcium salts. They have to be given in inordinately large quantities to induce appreciable diuresis in the nephrotic state and even then the effects are usually evanescent and disappointing. The administration of urea in doses of 40 to 60 Gm. a day is at times associated with profound diuresis. The number of failures, however, raises the question of how often these results with urea are happenstances.

The mechanism of action of these diuretics has been discussed with you before.

The mercurial diuretics have a place in the treatment of nephrotic edema and are apparently innocuous in the absence of severe renal failure, but they obviously should be administered repeatedly only if they produce significant diuresis.

Thyroid extract has been employed in the treatment of the nephrotic state but with disappointing results. Pyrogenic reactions induced by the intravenous injection of typhoid vaccine have also been used to initiate diuresis. This measure is occasionally successful, but the effects are usually transient and the therapy heroic.

Hypertonic glucose has been used in the hope of withdrawing water from the interstitial compartment, increasing the plasma volume temporarily, and offering more fluid to the kidney to increase glomerular filtration. Again, the results are usually disappointing.

In view of the low osmotic pressure of the plasma, it is natural that various osmotically active substances should have been employed, and the first of these was acacia. The occasional effectiveness of this agent cannot be doubted but it is unpleasant material. At times it causes marked pyrogenic reactions and these may, at least in part, be responsible for the diuretic effect. Furthermore, acacia is often stored in the liver and in the spleen. It also may induce thrombosis in cerebral and other vessels.

Plasma has at least theoretical value in treatment. Unfortunately, even temporarily beneficial results obtained following large quantities of this material are relatively few. It must be remembered that plasma not only contains physiological salt solution but also a large amount of sodium from citrate used in its preparation.

The most recent contribution to treatment in the nephrotic state is the use of salt-free human albumin, as employed by

Thorn, Armstrong and their co-workers. There are certain points which should be emphasized concerning the use of this product of plasma fractionation. First of all, it requires the intravenous administration of anywhere from 150 to 500 Gm. of human serum albumin to induce diuresis in most cases. When these massive doses of albumin are given (usually 50 Gm. daily), as much as 50 to 75 per cent of the material is excreted by the kidney. We have already indicated that heavy albuminuria probably results in the choking of the renal tubules with reabsorbed albumin. It seems possible that a very important part of the diuretic effect of serum albumin is that of effecting temporary tubular damage and thereby decreasing the reabsorption of sodium salts and water. This view receives support in the fact that diuresis in many patients takes place without a significant rise in the serum albumin level. That is to say, diuresis may not be dependent upon re-establishing the normal serum osmotic pressure, perhaps contrary to expectation. The economic factor in this treatment also deserves mention. In the process of plasma fractionation, it requires about 1,500 cc. of human blood to yield 25 Gm. of serum albumin. If 500 Gm. of albumin are required to treat one patient, 30 liters of blood or the equivalent of sixty ordinary transfusions must be employed. Furthermore, there is no assurance that the diuresis induced will be permanent and it seems improbable that this therapy fundamentally modifies the course of the underlying nephritis beneficially.

I am going to ask Dr. David Seegal, who with his group at the Goldwater Memorial and the Babies Hospital has had a wide experience with chronic nephritis, to discuss certain aspects of the nephrotic state.

DR. SEEGAL: Dr. Loeb has asked me to comment on certain data which we have accumulated. We agree that there are some patients who emerge from the neph-

rotic phase of glomerulonephritis and do not immediately enter the pre-uremic stage. Dr. Deming has reviewed the case histories of three of our patients who have returned to work following a prolonged nephrotic phase. The edematous periods of these patients were six months, one year, and two and one-half years. Since diuresis they have been followed for seven, five, and three years without any symptoms of nephrosis but in each case with persistent albuminuria and microscopic hematuria. It is thus seen that some individuals may pass through a severe nephrotic phase in the course of chronic glomerulonephritis and subsequently experience a reasonably normal life for as long as seven years.

We have come to believe that the nephrotic phase develops in the majority of patients with glomerulonephritis if the disease is prolonged. The frequency of this episode has led Dr. Bloom to emphasize its usefulness as a diagnostic criterion in defining the nature of the lesion in patients with renal failure.

I would like to raise several questions which would be brought up by Dr. Lyttle, with whom we were associated at the Babies Hospital. Dr. Lyttle has had experience with a large series of children with glomerulonephritis. He tells us that the large majority of children with acute nephritis recover completely. A few die of myocardial failure, severe hypertension with cerebral edema, or infection. When the disease in childhood progresses into the subacute and chronic stage, he has never seen the full nephrotic syndrome develop; that is to say, that children in the hospital with a nephrotic syndrome do not present a history of antecedent, clinically recognized acute glomerulonephritis.

Dr. Lyttle and I studied some of the immune reactions to the Group A hemolytic streptococcus in patients during various

stages of glomerulonephritis. One of our control groups consisted of children diagnosed as nephrosis. In contrast to the values found in normal individuals, thirty-six of thirty-eight children observed early in the course of nephrosis had abnormally low antistreptolysin titers; in the great majority, the value was less than 10 units. With remissions of the disease, when edema diminished and the serum albumin rose, the antistreptolysin titer returned to normal levels in fifteen of twenty patients. Eight relapses of nephrosis were observed in five patients with quiescent nephrosis. In seven of these relapses there was an associated drop in antistreptolysin titer from the normal to the abnormally low value. Despite the fact that the base line antistreptolysin titer is less than 10 units in these children with nephrosis, Group A hemolytic streptococcus infections produce a rise in antistreptolysin titer comparable to that expected in a normal child following a similar infection.

Studies of the immune response of adults with chronic glomerulonephritis by Dr. Earle in this clinic have shown that the base line antistreptolysin titer in the nephrotic phase is lower than that found in the same individuals in the non-edematous state. However, it is unusual to observe the low antistreptolysin titer values of nephrosis in the adult nephrotic phase. If we continue in this line of immunological thought, we might add that we have been puzzled by the rarity of the occurrence of pneumococcic peritonitis in our adult nephritics with ascites in contrast to the frequency of this episode in the nephrosis of children.

We hope that Dr. Kendall will comment on these immune reactions. Is there a possibility that the low antistreptolysin titers are related to a diminution in the gamma globulin content of the serum in nephrosis and the nephrotic phase of glomerulonephritis?

DR. KENDALL: There is no answer from our present information but it is a possibility.

DR. LOEB: I would also like to ask this question: If we are right in our assumption that serum albumin in the nephrotic state is not synthesized normally, and there are means at our disposal today by which that can be determined, is it possible also that the antistreptolysin is not synthesized normally?

DR. KENDALL: I think you can give certain answers to that. The fact that the antistreptolysin titer does go up following a streptococcal infection indicates that the individual does have the capacity for an immune response. The low basic antistreptolysin level in nephrotic patients may result from increased excretion of the globulin through the kidneys or from increased breakdown.

DOCTOR: The frequency of occurrence of pneumococcal infections in children with the nephrotic syndrome offers ample opportunity to study the immune response to the pneumococcus as well as to the streptococcus. Have studies been made in that direction?

DR. SEEGAL: A number of things are known about that, but the opportunity for making such studies is rapidly disappearing in naturally occurring pneumococcal infections. Since the introduction of penicillin therapy, none of these nephrotics has his pneumococcal infection long enough to evaluate immune responses. Dr. Lyttle believes that the immediate outlook for children with nephrosis is now excellent, though the development of nephritis with increasing renal insufficiency remains an ultimate hazard.

#### SUMMARY

The nephrotic syndrome is characterized by albuminuria, edema, hypoalbuminemia and hypercholesterolemia; frequently, it is

accompanied by a depression of the basal metabolic rate. It occurs most often in the course of chronic glomerulonephritis but may exist independently, as in lipoid nephrosis. Rarely, it is associated with secondary syphilis, leptospiral infections, amyloid disease, Kimmelstiel-Wilson syndrome or nephrotoxic poisons.

The term "nephrosis" was originally applied by Müller to degenerative lesions of the kidney primarily involving the renal tubules. The nephrotic state, however, occurs also with inflammatory diseases of the kidney. Furthermore, the significance of the tubular lesion in the etiology of the syndrome is open to question for it has been quite clearly shown that, in some instances at least, the tubular change may be the result and not the cause of albuminuria. It is obvious that some disturbance of the glomerular filter or in the serum proteins must be predicated to allow for the increased supply of protein presented to the tubules.

It was originally suggested by Epstein that the low serum albumin in the nephrotic state might result solely from urinary loss of serum proteins and that edema formation could be adequately explained on the basis of the Starling hypothesis of lowered osmotic pressure in hypoalbuminemia. But there is evidence that the Epstein hypothesis does not afford a complete explanation for the formation of edema. Thus diuresis may occur spontaneously without any increase in the low serum albumin levels. Excess protein intake usually does not restore the blood level of albumin even when positive nitrogen balance is established and body protein is stored.

It is now plain that leakage of albumin through the kidneys does not alone explain the manifestations of the nephrotic state, which evidently involves much more profound metabolic disturbances. Other factors evidently are at work. There is a renal de-

fect in the handling of the sodium ion by the kidney. Adrenal cortical hormones conceivably might play a part in water and sodium balance; and the rôle of the anti-diuretic hormone of the posterior pituitary gland has yet to be properly evaluated. The significance of hypercholesterolemia and lowered basal metabolic rate in the nephrotic state is not known, nor is it understood why the alpha globulins apparently are increased and the gamma globulins decreased in the blood.

Measures directed against the clinical abnormalities present in the nephrotic syndrome include diet high enough in protein to assure nitrogen balance; excessive feeding of protein accomplishes nothing more than restoration of body protein and may actually injure the renal tubules. Sodium intake is kept to less than 0.5 Gm. daily because more tends to promote edema. At this level, water may be taken freely; otherwise it, too, should be restricted. Of the diuretics, urea and mercurials are most often effective, but neither can be relied upon.

Efforts to promote diuresis by increasing the osmotic pressure of the circulating plasma have been unsatisfactory. Therapy with hypertonic glucose, acacia, human plasma or serum fall into this category. Salt-free for human albumin may be highly effective but has serious limitations. Thyroid extract rarely produces diuresis. In children, intercurrent infections, particularly pneumococcic peritonitis, respond promptly to penicillin. Syphilitic nephrosis also yields rapidly to treatment with penicillin.

Prognosis depends on the underlying disease. In lipoid nephrosis and chronic glomerulonephritis the duration of the nephrotic state cannot be predicted. In the former, however, the outcome is almost uniformly good today since formerly fatal infectious complications may now be adequately handled. Patients in the nephrotic phase of chronic glomerulonephritis, however, (and these comprise by far the largest proportion of cases) still face the ultimate fate of patients with the underlying disease.

# Clinico-pathological Conference

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## Coronary Artery Disease<sup>\*</sup>

**S**TENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

**T**HE patient was a fifty-three year old white, married farmer who entered the Barnes Hospital for the first time on February 9, 1943, complaining of abdominal pain and swelling of the ankles. The family history revealed that his mother had died of diabetes and one sister had died of an illness thought to have been tuberculosis. The patient had enjoyed excellent health with few exceptions until the onset of his present illness. He had done hard work as a farmer and had never had to limit his activity. At the age of twenty-four he had a probable Neisserian infection and for ten years he had had intermittent pain, radiating down the back of the left leg. He had consulted his family physician who told him he had "sciatica." His habits were good and his diet ample. His normal weight was 195 pounds but during the course of his illness he lost 45 pounds.

In 1940, the patient developed an easily reducible right inguinal hernia for which he wore a truss. In March, 1942, he had a sudden onset of severe pain at the site of the hernia which became irreducible. He became progressively ill and was admitted to a hospital in another community where an operation was performed. The patient was told that although the bowel had been discolored, none was removed. The hernia was repaired and recovery was uneventful. Following the operation, the patient noted

the onset of constipation and thereafter he had to use cathartics constantly. Several months later he began to have attacks of sharp, generalized, abdominal pain which were associated with considerable distention. During the attacks he could see and feel intestinal movement against the abdominal wall. The episodes were relieved following the passing of flatus. They bore no relation to meals or the time of day and were not accompanied by nausea, vomiting or the passage of blood in the stools. The patient found that the continual use of mineral oil and cascara diminished the severity of the attacks but he was forced to limit his diet to soft foods and liquids. Because of loss of weight and weakness, he had to stop working. Two weeks before entry to the Barnes Hospital, ankle swelling was noted and the patient became short of breath on exertion. He consulted several physicians but because his symptoms continued, he was admitted to the hospital on the Surgical Service.

At the time of entry, the temperature was 37°C., pulse 86, respirations 20, and blood pressure 120/80. The patient was a well developed but poorly nourished white male who did not appear acutely ill. The skin was loose and there was evident weight loss. The pupils reacted well to light and accommodation, and the fundi were normal. The ear drums were retracted and there was

<sup>\*</sup> From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.

slight hearing loss bilaterally. The teeth were in poor repair; many cavities were present and pyorrhea was extensive. The throat appeared normal. The chest was barrel-shaped and resonant to percussion. There were no abnormal findings on auscultation. Aside from distant sounds, examination of the heart was not remarkable. The abdomen was distended and the umbilicus was almost obliterated. Peristaltic waves were observed to move from left to right. There was marked tympany to percussion, and on auscultation, peristaltic sounds were heard at intervals. Questionable signs of fluid were noted in the flanks; no masses were felt. A long, well healed scar was present in the right inguinal region and the inguinal rings were lax on both sides. Transmitted impulses were felt bilaterally when the patient coughed. The right testis was larger than the left. The prostate was enlarged and boggy. Questionable early clubbing of the fingers was noted. There was pitting edema over the ankles and the feet. Neurologic examination was within normal limits.

The laboratory studies were as follows: Blood count: red cells, 4,160,000; hemoglobin, 11.4 Gm.; white cells, 12,800; differential count: eosinophiles, 1 per cent; stab forms, 2 per cent; segmented forms, 56 per cent; lymphocytes, 32 per cent; monocytes, 9 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 33 mg. per cent; total protein, 6.2 Gm. per cent; albumin, 3.6 Gm. per cent; globulin, 2.6 Gm. per cent; hematocrit, 40 per cent. Blood indices: mean corpuscular volume, 85 cubic micra; mean corpuscular hemoglobin, 29.5 gamma gamma; mean corpuscular hemoglobin concentration, 35 per cent. Electrocardiogram: T wave low in leads I, II, III; slurring and notching in all leads. Impression; myocardial damage.

Shortly after admission the patient was fluoroscoped. The heart was found to be transverse in position; the aorta was widened and lengthened and the diaphragms moved well. A subsequent stool examination was reported as guaiac positive. Proctoscopy was performed and a reddened mucosa without any gross lesions was seen. The patient was prepared for laparotomy by decompression with a Miller-Abbott tube; he received blood and plasma transfusions and was given sulfasuxidine by mouth.

On February 25, 1943, a laparotomy was performed. The omentum was found to be pulled over and was adherent to the splenic flexure of the colon. This attachment formed a band producing a hiatus into which the entire small intestine, with the exception of the duodenum, had herniated. The adhesions were divided and immediately thereafter the transverse colon and sigmoid were seen to fill with gas. Eight inches from the ileocecal valve the ileum was found to be stenosed by an annular fibrous constriction within its wall, the lumen being less than 0.5 cm. in diameter. An ileo-ileostomy was performed.

The postoperative course was uneventful until March 3, 1943, when it was noted that the patient's left leg was swollen. A diagnosis of thrombophlebitis was made and a left lumbar paravertebral block was performed; it had little effect on the swelling. Several days later the patient became short of breath and his pulse rose to 140; edema of the legs, thighs and sacrum was observed. The neck veins were distended. The heart was enlarged to percussion and the sounds were distant and of poor quality. The blood pressure fell to 110/95 and a few râles were heard at the lung bases. The patient was seen by a medical consultant and a diagnosis of myocardial infarction was made; it was confirmed by repeated electrocardiograms. The patient was treated with digitalis, a low salt diet, absolute bed rest, and



mercurial diuretics, and over a period of several weeks gradually improved. The pulse rate returned to normal, the sedimentation rate, which had risen during the acute episode, likewise returned to normal, and the patient became symptom-free. After five weeks of bed rest he was allowed to resume activity gradually, and was discharged on a maintenance dose of 0.1 Gm. of digitalis daily, a salt-free diet, and advised to limit his activity. He was instructed to return for follow-up examination.

Following discharge from the hospital, the patient continued to improve and he was able to do moderate labor on his farm without symptoms. He took 0.1 Gm. of digitalis a day and noted dyspnea only on rather marked exertion.

Six weeks before his second hospital admission he began to experience slight nausea, fleeting abdominal pain, weakness, increasing shortness of breath and increasing fatigue and palpitation. He developed slight ankle edema, more on the right. His appetite became poor, his abdomen increased in size and he gained approximately ten pounds. He was given ammonium chloride by his physician with some diminution in the amount of edema. The digitalis dosage was tripled but the major symptoms persisted and he was admitted to the hospital on the Medical Service on August 31, 1946.

Physical examination on entry revealed the temperature to be 37.4°C., pulse 80, respirations 28, and blood pressure 120/88. The patient was well developed and well nourished. He was dyspneic and moderately orthopneic; the lips were slightly cyanotic. Examination of the fundi revealed only narrowing of the arterioles. The neck veins were markedly engorged. Over the right lower lobe posteriorly, tactile fremitus was absent, breath sounds were diminished and there was flatness to percussion. Above this area and also at the left base posteriorly,

moist râles were heard. The heart was enlarged 15 cm. to the left of the midsternal line in the fifth left interspace; dullness extended 6 cm. to the right. The rhythm was totally irregular and there was a pulse deficit of 8. The sounds were faint. A soft systolic murmur could be heard over the entire precordium. The liver edge was moderately tender and was felt 10 cm. below the right costal margin. Signs of ascites were elicited on examination of the abdomen. The peripheral arteries were thickened; 1+ pitting edema of the extremities was present and a small easily reducible right inguinal hernia was noted.

The laboratory studies were as follows: Blood count: red cells, 5,080,000; hemoglobin, 14 Gm.; white cells, 13,750; differential count: juvenile forms, 4 per cent; stab forms, 4 per cent; segmented forms, 67 per cent; lymphocytes, 19 per cent; monocytes, 6 per cent. Urinalysis: negative except for a rare granular cast in the centrifuged sediment. Venous pressure: 230 mm. H<sub>2</sub>O. Circulation time: arm to tongue with Decholin, 40 seconds; arm to lung with paraldehyde, 18 seconds. Non-protein nitrogen: 23 mg. per cent. Roentgenogram of the chest: "There is considerable enlargement of the cardiac silhouette. The aorta is lengthened. The hilar shadows are prominent and the lung markings are coarse. There is partial obliteration of the right costophrenic angle with fluid." Electrocardiogram: low voltage in leads I, II, III; marked notching of the QRS complex; T waves low upright in leads I, II and III; occasional ventricular premature contraction.

The patient was placed in an oxygen tent on admission and a regimen was ordered which included 0.1 Gm. of digitalis daily, 2 Gm. of ammonium chloride four times daily, and a salt-free diet. On the day after entry the pulse was regular at 130. Several hours later the rate had fallen to 88 with an occasional ventricular premature con-

traction. The heart sounds were of poorer quality than on entry and a presystolic gallop rhythm appeared. Respiratory difficulty increased during the day and cyanosis became more prominent. On the evening of the second day the patient complained of substernal oppression and his dyspnea increased. The heart sounds at that time were faint and the rhythm was regular. No râles were heard on auscultation of the lungs. Fifteen minutes after these findings were noted, the patient gasped and died immediately.

#### CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: Although the main diagnostic problem in this case concerns the nature of the cardiac disease, three phases of the patient's illness are worthy of comment: first, the identity of the gastrointestinal lesion which led to the first admission; second, the postoperative complication which was interpreted as cardiac in origin; and finally, the nature of the terminal episode. Dr. Kenamore, would you comment on the lesion described in the terminal ileum at the time of the laparotomy?

DR. BRUCE D. KENAMORE: I believe the lesion was benign for the patient lived three years after the operation; malignancies of the small bowel lead to death in a shorter period of time. Of the benign lesions, either regional ileitis or a non-malignant neoplasm must be considered.

DR. WOOD: The lesion was described as being constrictive. May a tumor cause such constriction?

DR. KENAMORE: Yes. Fibromatous tumors of the small intestine, in particular, may impinge on the lumen and give rise to intestinal obstruction.

DR. WOOD: Would you comment on the time relationships in this case? The patient's symptoms all developed after his operation for hernia. Do you think it possible that, as

a result of the first operation, pathologic changes occurred which ultimately led to the second operation?

DR. KENAMORE: It is conceivable that postoperative adhesions caused intestinal obstruction but that diagnosis seems less likely to me than the first two I mentioned. Regional ileitis often involves a larger portion of the small intestine than was described here and the lesions are frequently multiple.

DR. CARL V. MOORE: I have seen annular constrictions of the small intestine at post-mortem examination for which there was no definite explanation. They were thought to be due to injury or infection but were not typical of regional ileitis.

DR. PALMER H. FUTCHER: Dr. Moore, would you comment on the etiology of regional ileitis?

DR. ROBERT A. MOORE: There is no proven cause of regional ileitis; much of the evidence suggests that the process is associated with lymphatic obstruction.

DR. WOOD: Let us now consider the nature of the postoperative episode. The patient exhibited many of the signs of congestive heart failure. Edema was particularly prominent in the left leg and there was dullness to percussion at the right lung base but at no time did the patient cough up blood. Dr. Smith, would you comment on these findings?

DR. JOHN R. SMITH: In all probability there was a diminution or obstruction of the coronary flow resulting in a myocardial infarction with associated cardiac failure. The fact that the edema was confined to the left leg is not too remarkable; not infrequently patients in congestive failure have edema only in one leg and in such instances it is usually the left which is involved.

DR. WOOD: Is coronary occlusion common following operation?

DR. SMITH: Coronary occlusion may occur following an operation, particularly in patients with arteriosclerotic coronary

artery disease. It has been shown that when the blood pressure falls following an operation, the coronary blood flow may be reduced to such an extent that myocardial infarction results even without complete occlusion of the lumen of an artery. Such a sequence of events might have transpired here.

DR. WOOD: Dr. Schroeder, what are your views on the occurrence of edema affecting the left leg in congestive heart failure?

DR. HENRY A. SCHROEDER: I have had an experience similar to that recounted by Dr. Smith; namely, that edema begins in the left leg in congestive heart failure. I do not know the reason although in this case the patient may have had an old healed thrombophlebitis with impaired return of venous blood from that extremity.

DR. WOOD: In my experience unilateral edema is rather rare in congestive heart failure.

DR. SMITH: I would alter my statement and say that edema is often more intense in the left leg, though usually present in both.

DR. SCHROEDER: The clinicians who took care of this patient must have postulated that he had a deep pelvic thrombophlebitis since they did a left lumbar paravertebral block. Thrombophlebitis with a pulmonary embolism must also be considered.

DR. WOOD: Is it possible to differentiate pulmonary infarction from myocardial infarction on the basis of electrocardiographic changes?

DR. EDWARD MASSIE: The electrocardiograms in this case favor the diagnosis of myocardial infarction.

DR. WOOD: Would you discuss the tracings, Dr. Massie?

DR. MASSIE: In the first tracing, taken in 1943, the voltage was low in leads I, II and III and there was a sinus tachycardia. On deep breathing the QRS segment became upright in lead III. The T wave in

lead I was low but upright and that combined with the low voltage led to the interpretation of myocardial damage. An electrocardiogram several days later showed definite changes; the voltage was still low but the T wave in lead I had become isoelectric, and a definite Q wave appeared in leads CF<sub>2</sub> and CF<sub>4</sub>. These changes strongly suggest a recent myocardial infarction. In the third electrocardiogram the changes were even more indicative of myocardial infarction for the S-T segment in lead IV became elevated and the rate increased to approximately 140. The next tracing showed T<sub>2</sub> becoming upright, T<sub>1</sub> isoelectric or diphasic, and a Q wave in lead I. The other leads were approximately as before. In the final record S-T<sub>1</sub> was rounded, T<sub>1</sub> inverted, T<sub>2</sub> less upright, and there was rounding and dipping of the S-T segment in CF<sub>4</sub>. These changes are indicative of an acute myocardial infarction. The changes in pulmonary infarction may be somewhat similar but they are usually more precipitous.

DR. WOOD: This patient had no pain. How frequent is myocardial infarction without pain?

DR. MASSIE: Frequently patients are seen who have an abnormal electrocardiogram as, for example, indicated by the finding of left bundle branch block. In reviewing the history no episode compatible with coronary occlusion can be found but statistically most of these patients have had one. The state of clarity of the patient's sensorium is important in this regard. An ambulatory patient is usually aware of a coronary occlusion but in this patient, whose infarction occurred postoperatively, it is possible that he had not sufficiently recovered from the operative procedure to detect the pain incident to infarction.

DR. WOOD: This patient had a blood pressure of 110 over 95 and therefore a pulse pressure of only 15. Would you comment on this finding, Dr. Massie?

DR. MASSIE: Such a pulse pressure is quite low and difficult to interpret in this case, particularly if borne out by subsequent readings. A plausible explanation is that the patient's diastolic pressure was usually about 95 and that his systolic pressure fell postoperatively because of the coronary occlusion.

DR. SCHROEDER: A low pulse pressure is seen not infrequently when the cardiac output diminishes following myocardial infarction. The elevated diastolic pressure suggests generalized vasoconstriction resulting from a lowered cardiac output, anoxia and a state of impending shock.

DR. WOOD: Then you believe that this blood pressure is quite consistent with myocardial infarction?

DR. SCHROEDER: As a matter of fact, I believe it to be fairly characteristic of a severe infarction.

DR. WOOD: The general consensus of opinion seems to favor a myocardial infarction for the postoperative episode. Are there any other comments?

DR. C. V. MOORE: Frequently cases of myocardial infarction with associated cardiac failure in which digitalis is used progress to a fatal termination, and it is always pointed out that digitalis may have been toxic and thus detrimental in such instances. It should be mentioned, therefore, that this patient, although he had a myocardial infarction, apparently tolerated digitalis very well.

DR. WOOD: Dr. Smith, would you have given this patient digitalis with these clinical findings and a tentative diagnosis of myocardial infarction?

DR. SMITH: As a result of recent investigations, carried out in our laboratory at the suggestion of Dr. Schroeder, I have come to the conclusion that digitalis should be avoided in cases of myocardial infarction with failure unless the cardiac insufficiency

is extreme, and then digitalis should be given with great caution.

DR. SCHROEDER: I agree with Dr. Smith.

DR. C. V. MOORE: I would have withheld digitalis in this instance but I do believe that there are a large number of patients in similar circumstances who tolerate digitalis well.

DR. SCHROEDER: I believe that, under such circumstances as these, the patient should be put to bed, kept absolutely quiet and should be given oxygen. When there is necrosis of cardiac muscle, irritable foci are set up at the slightest provocation. Furthermore, this tendency is exaggerated by the coronary spasm and anoxia. To give a drug which is a cardiac stimulant and also a myocardial irritant seems to me to be unwise.

DR. WOOD: Dr. Smith, do you think that the episode which terminated this patient's life was a second myocardial infarction?

DR. SMITH: Yes, it may well have been. However, it is possible that there was such a degree of coronary arteriosclerosis that there was myocardial insufficiency without infarction.

DR. WOOD: What is your feeling on this point, Dr. Massie?

DR. MASSIE: I believe coronary insufficiency without a fresh myocardial infarction was the most likely cause of the terminal episode, but there is not sufficient evidence to enable one to be dogmatic as to the cause of death.

DR. SMITH: A pulmonary infarction due either to an embolus or a thrombosis of the pulmonary artery must be considered, for the patient had a sudden fall in the pulse rate and became cyanotic and very dyspneic.

DR. SCHROEDER: I should like to suggest that digitalis intoxication may have led to the patient's exitus.

DR. WOOD: That is a good suggestion. The patient's digitalis dose had been doubled or trebled before he entered this

hospital. When he was admitted, his pulse was slow and totally irregular. He subsequently had a bout of tachycardia with possible auricular flutter which reverted eventually to a normal rhythm.

DR. SCHROEDER: Two-tenths of a Gm. of digitalis daily, which was the dose this man was taking, is usually tolerated by most patients but on some occasions it may give rise to toxicity.

DR. WOOD: Are there any other suggestions?

DR. MASSIE: A mural thrombus with detachment and escape into the pulmonary circulation may have led to a pulmonary infarction.

DR. MICHAEL M. KARL: Is it postulated that the increase in the patient's heart size was due to myocardial insufficiency?

DR. SCHROEDER: If the coronary arteries are narrowed and the myocardial muscle is damaged, the heart may be greatly dilated.

DR. WOOD: It is often stressed in text books that in arteriosclerotic coronary artery disease the heart is usually small. I believe, however, that Dr. Schroeder's statement is correct. Would you agree with it, Dr. Moore, from a pathologic standpoint?

DR. R. A. MOORE: In certain cases of coronary arteriosclerosis, dilatation is seen and may actually go on to hypertrophy.

DR. WOOD: In summary, it may be said from the present discussion that the staff favors the diagnosis of a benign lesion in the ileum. Either tumor or scarring resulting from previous ileitis may have caused the stricture described at operation. The illness in the postoperative period was probably a myocardial infarction and the terminal illness appeared to be due to coronary insufficiency, with congestive heart failure possibly precipitated by a fresh myocardial infarction. Pulmonary infarction remains a possibility and digitalis intoxication cannot be ruled out.

*Clinical Diagnosis:* Benign stricture of the

ileum; arteriosclerotic coronary artery disease with old and possibly recent myocardial infarction; cardiac insufficiency; ?pulmonary infarction, and ?digitalis intoxication.

#### PATHOLOGIC DISCUSSION

DR. OSCAR N. RAMBO: At autopsy the major findings were limited to the thorax. There were 1,700 cc. of amber fluid in the right pleural cavity and 500 cc. in the left pleural cavity. Part of the pleural space about the upper lobe of the right lung was obliterated by fibrous bands. The pericardial fluid was clear and of normal volume. *In situ*, the heart was greatly dilated and of flabby consistency; the transverse diameter was increased. On the epicardial surface there were several smooth, translucent areas with slight fibrous thickening. Beginning at the apical incisure and capping the apex of the left ventricle there was an area of softening 4 cm. in diameter. In this region the myocardium was only 5 mm. thick and was white and fibrous. Another elongated area of softening was found adjacent to the interventricular sulcus posteriorly.

On opening the heart the epicardium about the apex of the left ventricle was white, thick and fibrous. There was fibrous thickening of the anterior leaflet of the mitral valve and of the bases of the aortic cusps, the latter to such a degree that they projected slightly into the lumen of the valve. Examination of the coronary arteries showed normal ostia and yellow, elevated, fibrous plaques in the intima. At a point 23 mm. from the ostium, the lumen of the anterior descending branch of the left coronary artery was almost completely filled by an adherent, grayish-white, firm mass which extended for 10 mm. Thirty mm. from its ostium the lumen of the circumflex branch also appeared to be occluded by a soft, homogeneous, but adherent, reddish-gray mass. The lumen of the

right coronary artery was completely occluded 23 mm. from the ostium by a thrombus which was dark red and partially organized. In the right atrial appendage there was a firm, friable and laminated grayish-red mass which was organized and adherent. It measured 2 by 2 cm.

The kidneys were slightly enlarged, the right weighing 175 Gm. and the left 210 Gm. The surfaces were finely granular and the pyramids, on section, were dark purple in color. Examination of the site of the intestinal anastomosis showed no evidence of tumor. The anastomosis was 31 cm. proximal to the ileocecal valve and the stoma was 6 cm. in diameter. The prostate measured 43 by 35 by 38 mm. The cut surface presented bulging, yellow-white, translucent, nodular areas 5 to 10 mm. in diameter. There were adhesions between the spermatic cord and the right inguinal canal.

DR. R. A. MOORE: From a gross standpoint the findings constitute a fairly characteristic example of advanced coronary arteriosclerosis as evidenced by occlusion of the left descending, the left circumflex and the right coronary arteries. Thus the major part of the blood supply to the myocardium had been interfered with. In addition, there was an old infarct at the apex of the left ventricle and a more recent infarct in the posterior wall of the left ventricle.

Turning to the microscopic sections, Figure 1 shows a cross section of the left coronary artery. The lumen is filled with a mass of tissue containing vascular spaces and represents a completely recanalized thrombus. Figure 2 lends support to the fact that the occlusion was due to the recanalized thrombus rather than to an arteriosclerotic plaque for numerous macrophages filled with hemosiderin pigment are seen; these are generally assumed to be evidence that red cells had been present.



FIG. 1. Cross section of the left coronary artery showing recanalized thrombus in the lumen.

In the walls of the recanalized channels smooth muscle may be noted. The next section (Fig. 3) is taken from the left ventricular wall near the apex. There is almost total destruction so that only a few bundles of muscle fibers remain. The infarct is old, probably of months' duration. Figure 4 shows an area through an old scar. All evidence of myocardial structure has been removed and only a few blood vessels remain in the fibrous tissue. In Figure 5 a section of the right coronary artery is seen; it shows a typical arteriosclerotic plaque in the wall. The lumen is occluded by a very recent thrombus about which there is no organization; it has, therefore, been present for only a few days. In Figure 6 a papillary muscle of the mitral valve shows evidence of acute infarction adjacent to an area of old infarction. There is considerable cellular infiltration and although the infarct is not as old as the one demonstrated previously, there are other changes in the muscle which are of a duration of twenty-four to forty-eight hours. Thus there is evidence of at least two changes; first, an old infarct of months' duration and second, one which had occurred only a short time before death. Figure 7 is taken through the right atrial wall at the site of infarction. The thrombus found in the atrial appendage was typical of those not infrequently observed at the site of an old infarction.



FIG. 2. Higher power view of the thrombus seen in Figure 1, showing numerous macrophages filled with hemosiderin.

In a section of the kidney (Fig. 8) there are the changes of minimal arteriolar nephrosclerosis. The blood vessels are slightly thickened and the basement membrane of the glomerular capillaries is thickened but there is no significant increase in the amount of connective tissue. There is no evidence of a chronic destructive renal lesion. The prostate exhibited the changes of nodular hyperplasia.

In attempting to correlate the clinical and pathologic findings, let us consider the history briefly. No lesion at autopsy was found which could be related to the Neisserian infection which the patient had in his youth. The right inguinal hernia resulted in adhesions between the cord and the inguinal canal on that side. These were broken with some difficulty. At the time of the laparotomy the omentum was found to be pulled over to the splenic flexure of the colon. The capsule of the spleen was

thickened and there were adhesions between the splenic capsule and the diaphragm—a perisplenitis. The ileum was stenosed by an annular fibrous constriction within the wall, but at autopsy the only finding was an ileo-ileostomy with a stoma which was obviously functioning well. There was no pathologic change to indicate the nature of the original lesion. Although the left leg was more edematous than the right, the left common iliac and left external iliac veins were not the site of thrombophlebitis.

The anterior myocardial infarction was of an age consistent with the patient's episode in the postoperative period. The cardiac failure may be correlated with findings indicating chronic passive congestion of the viscera. The heart, which weighed 550 Gm., was unusually dilated; the soft systolic murmur which was heard over the precordium was probably caused by thickening at the base of the aortic valve. The liver which on physical examination extended 10 cm. below the costal margin, was noted to extend down 5 cm. at the time of autopsy. The kidney showed only slight nephrosclerosis and chronic passive congestion. Thus, the clinico-pathologic correlation in this case is quite satisfactory. The pathologic anatomist cannot demonstrate digitalis intoxication with certainty, but in experimental animals and in some patients hemorrhagic foci in the myocardium are seen under such circumstances. Such a lesion was not observed here.

*Pathologic Diagnosis:* Arteriosclerosis of the coronary arteries, advanced; organized thrombus in the anterior descending branch of the left coronary artery; partially organized thrombus in the circumflex branch of the left coronary artery; healed infarcts of the anterior wall of the left ventricle and anterior part of the septum and of the posterior wall of the left ventricle; thrombus with beginning organization in the posterior

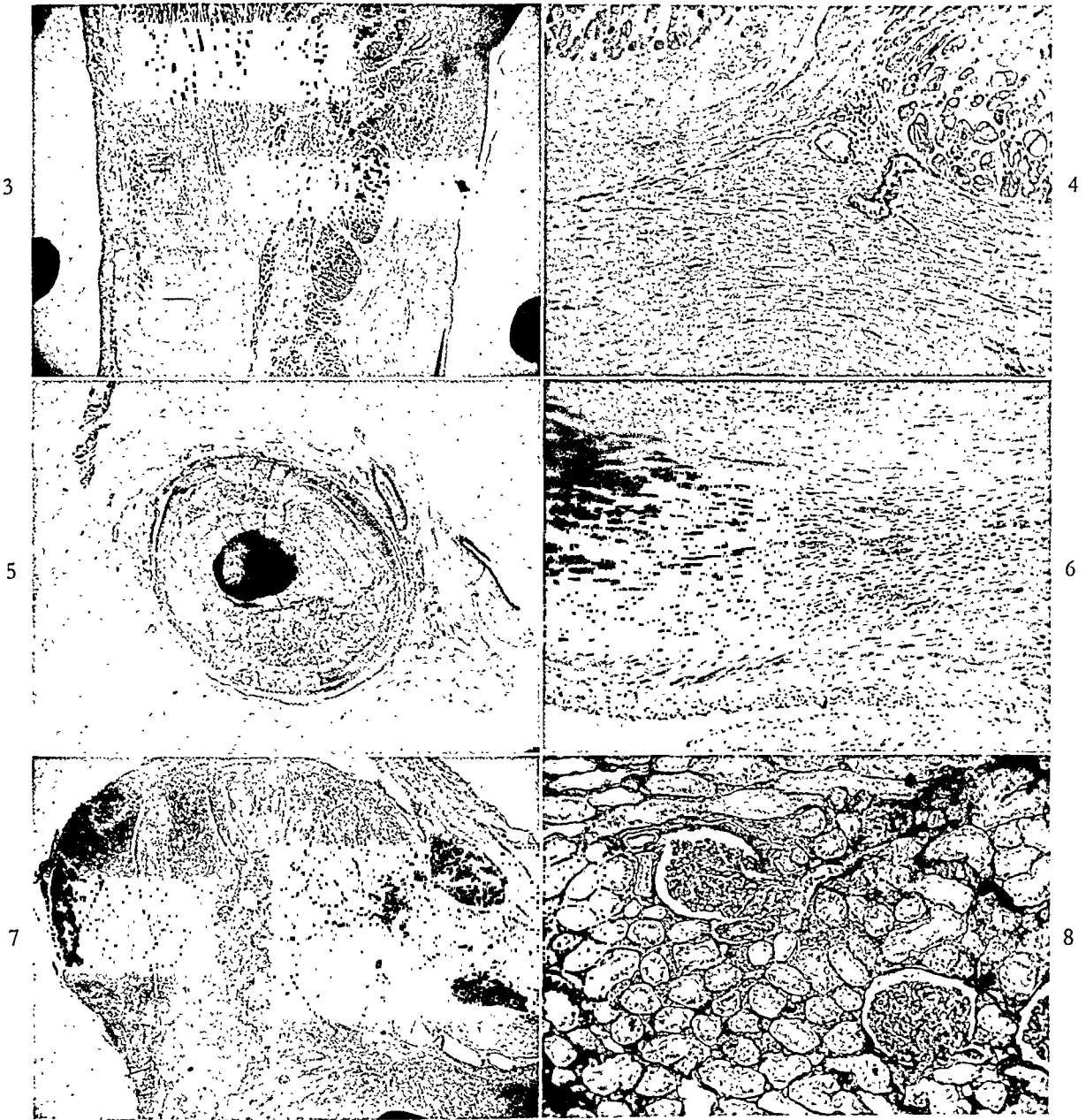


FIG. 3. Section from the left ventricular wall through the area of infarction.

FIG. 4. Another section of the myocardium through an area of old infarction.

FIG. 5. A cross section of the right coronary artery showing an arteriosclerotic plaque in the wall.

FIG. 6. Section of a papillary muscle of the mitral valve. Note the changes of both recent and old infarction.

FIG. 7. Section through the right atrial wall at the site of infarction.

FIG. 8. Section of the kidney exhibiting changes of minimal arteriolar nephrosclerosis.

descending branch of the right coronary artery; organizing infarct of the right auricular appendage; mural thrombus, right atrial appendage; hypertrophy and dilatation of the heart (550 Gm.); arteriolar nephrosclerosis, slight; hydrothorax, bilat-

eral; chronic passive congestion of the liver and kidneys, moderate; of the spleen, slight; sclerosis of the anterior leaflet of the mitral valve and cusps of the aortic valve at the bases; side-to-side anastomosis of ileum; nodular hyperplasia of prostate.



# Case Report

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## Subcutaneous Emphysema in Vomiting of Pregnancy

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**S**UBCUTANEOUS emphysema, usually secondary to mediastinal emphysema, has been reported as occurring in a variety of conditions, including injury, following operations, heavy lifting, straining at stool, childbirth, anesthesia with coughing, in asthma, bronchitis, after inhaling foreign bodies, in whooping cough and pneumonia, as well as spontaneously in pulmonary tuberculosis.

The present theory as to the causation is that air may reach the mediastinum and from there the subcutaneous tissues through (1) fascial planes of the neck, (2) perforation of the trachea, bronchus or esophagus, (3) from the retroperitoneal space, and (4) from the interstitial tissue of the lung. The exact mechanism of the entry of air from the air passages into the tissue is usually not known. It is assumed that the effort of coughing or straining produces a break in the continuity of the mucous membrane and that air is thus forced into the interstitial tissue whence it proceeds to the mediastinum and if sufficiently severe, into the subcutaneous tissues. When subcutaneous emphysema occurs, it does so practically always in association with air in the mediastinum. Hamman recently reviewed the literature and gave an excellent summary of present knowledge in regard to this condition.<sup>1</sup>

The following case is of interest because the patient developed widespread and marked subcutaneous emphysema without mediastinal emphysema and also because,

although the factor which apparently produced it (vomiting of pregnancy) continued, the emphysema occurred only once.

### CASE REPORT

Mrs. H., age twenty, was admitted to an Army General Hospital because of pain in the neck, shoulders and chest, together with swelling of the face, chest and back. The patient's last menstrual period was three months before admission. One month prior to admission she began to have nausea and vomiting which was not marked until five days prior to hospitalization. At this time, the nausea and vomiting were severe with considerable retching, especially in the morning. Two days before admission she developed a sudden pain in the neck during a vomiting spell. Swallowing became difficult and the pain rapidly spread over the shoulders, up into the neck and face, and was accompanied by swelling of the tissues. On admission the patient was in moderate distress, markedly dehydrated and complaining of a feeling of tightness in the throat and chest. On examination the patient presented a striking appearance with marked swelling of the face, neck, back and chest, beginning at the malar prominence on both sides of the face, extending down the neck over the shoulders as far as the deltoid insertions and to the lower rib margins, front and back. Slight cyanosis was present but there was no marked dyspnea. Definite crepitation was felt over the entire area of swelling. The lungs were normal on physical examination as was the heart. Although the air in the tissues produced crepitation on auscultation, there were no abnormal sounds arising in the mediastinum or lungs. Hamman's sign was absent. The physical ex-

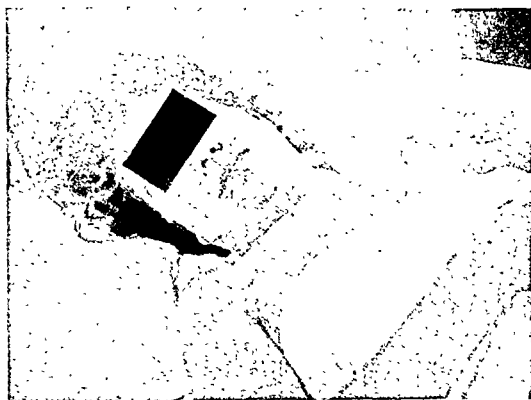


FIG. 1. Appearance of patient upon admission.

amination, otherwise, revealed nothing abnormal. Pelvic examination revealed enlargement of the uterus, consistent with pregnancy of three months' duration. There were no abnormal findings in the blood or urine. X-ray studies revealed the subcutaneous emphysema in the areas mentioned but no abnormal collections of air could be made out anywhere within the chest. Since the patient's condition was good and there was no respiratory embarrassment, no special treatment for the subcutaneous emphysema was given. The patient was very much relieved when an explanation for the situation was given to her. Although the nausea and vomiting continued for several days after admission to the hospital, the subcutaneous emphysema steadily decreased and was completely absent at the end of fourteen days.

#### SUMMARY

Marked and widespread subcutaneous emphysema occurred in a young woman in



FIG. 2. Appearance ten days later.

her first pregnancy, apparently due to the stress of vomiting. No source for the development of the emphysema could be discovered, and the condition subsided promptly in spite of the fact that the vomiting continued. This suggests the presence of some defect which, having allowed the escape of air into the subcutaneous tissues, became inoperative although the mechanism of stress continued.

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1. HAMMAN, LOUIS, Mediastinal emphysema. *J. A. M. A.*, 128: 1, 1945. 2703 Oak Lawn Ave.

## Immunization against Influenza

SINCE the initial discovery of human influenza virus in 1933 by Smith, Andrewes and Laidlaw,<sup>1</sup> subsequently designated virus A, and the later discovery of influenza virus B in 1940 by Francis,<sup>2</sup> many fundamental investigations on various aspects of epidemic influenza have served to provide a sound scientific basis for the recent development of means for immunization against the natural disease. Among these investigations may be mentioned the early demonstration that the virus is pathogenic for Swiss mice; the subsequent finding that the virus can readily be cultivated in the allantoic fluid of the chick embryo; and the observation that influenza virus grown in the allantoic fluid of the chick embryo can be adsorbed by the erythrocytes of the embryo and then readily eluted from the red blood cells.<sup>3</sup> Equally important are a series of immunologic studies which have shown that a rise in antibody titer occurs following natural infection; that a similar increase in titer can be induced artificially by subcutaneous injection of active or inactive virus; and that mice can be immunized against an otherwise fatal infection.

Finally the development of methods for laboratory proof of diagnosis, either through recovery and identification of virus or demonstration of rise in antibody titer following recovery from infection, has served a dual purpose in further elucidating

the epidemiological and clinical characteristics of influenza. First, by the use of these methods it has been possible to show the cyclic recurrence of epidemics of influenza A every two or three years and of influenza B every four to six years and to establish the fact, long suspected, that localized outbreaks of influenza and even sporadic, isolated cases occur during interepidemic periods. Secondly, it has been possible to confirm the opinion, formerly based on insecure clinical grounds, that there is a wide variation in the severity of epidemic influenza ranging from mild infections, indistinguishable clinically from other mild respiratory diseases, to severe fulminating cases reminiscent of those seen in the pandemic form of the disease. In the final analysis, as pointed out by Salk and Francis,<sup>4</sup> the foregoing contributions and, indeed, many others were essential prerequisites for success in devising a practical method of immunization and in demonstrating its effectiveness.

Based on the investigations briefly summarized above, the Army Epidemiological Board through its Commission on Influenza under the direction of Dr. Thomas Francis, Jr., undertook in 1941 to determine whether in fact a practical method for controlling epidemics of influenza could be developed. In 1942, Francis and Salk<sup>5</sup> devised a simplified method for the preparation of a concentrated and reasonably purified vaccine containing approximately equivalent amounts of influenza virus A and B. This vaccine was then demonstrated to be

<sup>1</sup> SMITH, W., ANDREWES, C. H. and LAIDLAW, P. P. A virus obtained from influenza patients. *Lancet*, 2: 66, 1933.

<sup>2</sup> FRANCIS, T., JR. A new type of virus from epidemic influenza. *Science*, 92: 405, 1940.

<sup>3</sup> HIRST, G. K. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J. Exper. Med.*, 75: 47, 1942.

<sup>4</sup> SALK, J. E. and FRANCIS, T., JR. Immunization against influenza. *Ann. Int. Med.*, 25: 443, 1946.

<sup>5</sup> FRANCIS, T., JR. and SALK, J. E. A simplified procedure for the concentration and purification of influenza virus. *Science*, 96: 449, 1942.

capable not only of stimulating the production of antibodies and actively immunizing mice, but also of furnishing definite protection in human beings against experimentally induced influenza A<sup>6</sup> and influenza B.<sup>7</sup>

In the fall of 1943, with the expectation that there might be an epidemic of influenza A, a controlled study in Army Specialized Training Program units was undertaken. As a result it was determined that vaccination with a single subcutaneous injection of 1.0 cc. of a concentrated inactivated influenza vaccine given shortly before an influenza type A epidemic exerted a marked though not complete protective effect, the incidence of influenza being 3.2 times as great in the controls as in the vaccinated. There is evidence to suggest that this difference is not an adequate measure of the effectiveness

<sup>6</sup> FRANCIS, T., JR., SALK, J. E., PEARSON, H. E. and BROWN, P. N. Protective effect of vaccination against induced influenza A. *Proc. Soc. Exper. Biol. & Med.*, 55: 104, 1944.

<sup>7</sup> SALK, J. E., PEARSON, H. E., BROWN, P. N. and FRANCIS, T., JR. Protective effect of vaccination against induced influenza B. *Proc. Soc. Exper. Biol. & Med.*, 55: 106, 1944.

of vaccination because of an apparent reduction in the attack rate in the unvaccinated controls as compared with the attack rate in groups in which none of the population had been vaccinated.<sup>4</sup>

Results comparable to those described above for influenza A have now been recorded<sup>8</sup> during the epidemic of influenza B in the late fall of 1945 with a ratio of cases in vaccinated versus unvaccinated of 1 to 9.

The fact that human resistance to influenza A and B can be greatly enhanced by vaccination with a single dose of inactivated vaccine would now appear to be well established. How frequently vaccination should be performed for the effective control of epidemics, whether means may be devised for enhancing and prolonging individual protection, and the possible effectiveness of vaccination in the face of severe pandemic influenza are problems still requiring solution.

F. G. BLAKE, M.D.

<sup>8</sup> FRANCIS, T., JR., SALK, J. E. and BRACE, W. M. Effect of vaccination against epidemic influenza B. *J. A. M. A.*, 131: 275, 1946.

# Book Reviews

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A NEW textbook<sup>1</sup> on the subject of peripheral vascular disease is a credit to the authors and the Mayo Clinic. Comprehensive, detailed, accurate and sane it is clearly phrased and thoughtfully arranged. With little doubt, it takes its place as the best single volume covering this aspect of medicine.

The three authors and eleven other contributors are all experienced in their specialties and many have carried out independent investigations in them. The tone of the volume reflects this background since it is at once authoritative yet careful to delineate known from unknown. The approach is modern, too, in the attempted correlation with physiological mechanisms. Of particular interest to the practitioner is the detailed and careful consideration given to the evaluation of the many and often useless types of therapy.

Thirty-one chapters comprise the volume. The first begins with a definition of terms; the last ends with the medicolegal aspects of these diseases. In between may be found extensive discussions of Raynaud's phenomena, the scleroderma group, thrombosis, embolism, arteriosclerosis obliterans, Buerger's disease, the arteritides, aneurysms, fistulas, vascular tumors, the range of venous abnormalities and their treatment, and a consideration of lymphedema. Each chapter subdivides the subject under consideration into its logical components so that reference to a particular point (with the aid of an excellent index) is made easier. A list of important and modern references is given at the end of each chapter. The illustrations are technically good, well chosen and aid

the text. Little more could be expected from them.

Here then is a well bound and printed book which is the finest single volume yet to appear on the subject of peripheral vascular disease.

F.K.H.

IN spite of wars and political upheavals, in spite of elaborate and difficult experimental procedures, in spite of the many tests required to check and re-check each new development before passing on to another, the original and painstaking discoveries of the group working under Professor Bernardo A. Houssay in Buenos Aires have stood the test of time and are unique examples of the proper and true scientific approach.

Dr. Dexter, who at one period was a collaborator in many of these studies, has done a magnificent job in his presentation and translation of the book on renal hypertension, first published in 1943.<sup>2</sup> Following a prologue by Prof. Houssay, one is carried step by step through the entire field of experimental hypertension and its possible relationships to hypertensive vascular disease in man. Each chapter, with detailed and critical reviews of the world-wide literature on the subject, is carefully organized, and contains a concise résumé at the end. The illustrations are many but invariably self-explanatory and clearcut.

Although one may take exception to some of the conclusions and interpretations of the authors in their attempt to place essential hypertension on a purely renal humoral basis, the reader will find no better source through which to become acquainted "with

<sup>1</sup> PERIPHERAL VASCULAR DISEASES. By Edgar V. Allen, Nelson W. Barker, Edgar A. Hines, Jr. with associates in the Mayo Clinic and Mayo Foundation. Pp. 871 with 386 illustrations. 7 in color. Philadelphia, 1946. W. B. Saunders Company. Price \$10.00.

<sup>2</sup> RENAL HYPERTENSION. By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Muñoz, and Alberto C. Taquini. Translated by Lewis Dexter. Pp. 451, with 93 illustrations. Springfield, Illinois, 1946. Charles C. Thomas. Price, \$6.75.

the views of those who have perhaps been responsible more than any other group for the clarification of the renal humoral pressor mechanism."

This volume is a fitting tribute to Professor Houssay and his eminent co-workers and should be obligatory reading for those individuals interested in any aspect of hypertension.

G.A.P.

**T**HIS practical book<sup>3</sup> is a review of peptic ulcer in which diagnosis and treatment are emphasized. There are long chapters on roentgen diagnosis, with excellent illustrations, and on differential diagnosis and medical therapy. The various theories on the etiology of ulcer are critically reviewed and the physiological mechanisms of the symptoms of the disease are discussed. An interesting chapter on experiences with the dyspeptic soldier is included, in which a reconditioning program is described which enabled 70 per cent of the patients to continue in military service.

In some of the controversial problems of treatment, the authors lean toward conservatism, and as an example, they favor delayed feeding in cases of gross hemorrhage. They also favor the simpler operative procedures in surgical treatment and state that they have frequently had disappointing results with subtotal gastrectomy.

While one may disagree at times with the opinions stated, this should not obscure the fact that this is a comprehensive, well written book which will be useful to students and practitioners.

C.A.F.

**T**HE organization and format of the second edition of this widely used text<sup>4</sup> is the same as the first edition. Revision of the text is largely to bring it up to date. The *Lactobacillus casei* factor

<sup>3</sup> PEPTIC ULCER—ITS DIAGNOSIS AND TREATMENT. By I. W. Held, M.D. and A. Allen Goldbloom, M.D. Springfield, Ill., 1946. Charles C. Thomas. Price \$6.50.

<sup>4</sup> CLINICAL HEMATOLOGY. By Maxwell M. Wintrobe, M.D. 2nd ed., 862 pp. Philadelphia, 1946. Lea and Febiger. Price \$11.00.

("folic acid") and the use of the nitrogen mustards are discussed. There is a readable account of the Rh factor. Advances in mineral and porphyrin metabolism, in large measure acquired from applications of the isotope technics, are included in a new chapter on the metabolism of the erythrocyte.

The success of the first edition is perhaps an indication of the author's achievement of objectives stated in the preface. These were "to bring together the accumulated information in the field of hematology in a systematic and orderly form, to sift the important from the less significant, to describe the newer methods which are of practical value, and to make note of those which are less essential, to outline details of differential diagnosis, to describe the indications for and methods of treatment, and to make clear as far as present knowledge permits the nature of the underlying physiologic disturbances."

The first six chapters are devoted to the development, physiology and chemistry of the formed elements and to the blood as a whole. The principles and technics of blood examinations are described in the next chapter. Other methods are discussed critically and in detail in chapters of which they form a logical part. A detailed presentation of the pathology, pathologic physiology, differential diagnosis and treatment of the anemias is arranged in the next six chapters in the classification most useful to an understanding of their causes and management. The remaining chapters are discussions of polycythemia, the purpuras, hemophilia, leukemia, tumor and tumor-like conditions involving the blood-forming organs, agranulocytosis, and infectious mononucleosis.

The text is comprehensively documented by more than 110 pages of references. The charts, tables and illustrations are, for the most part, helpful.

This book can be recommended to physicians and students as authoritative, detailed and readable.

R.A.K.

**A**NTHOLOGIES are frequently best sellers so that new ones constantly appear. Here is the first entirely concerned with the doctors, nurses and patients met in contemporary fiction. Thirty five selections ranging from short stories to excerpts from longer works of thirty-four authors make up this collection.

The pieces vary widely: humor and pathos, fantasy and realism, comedy and tragedy, love and hate all are represented. One can wander through the book certain that there is something to fit the mood of the moment. While the difference in subjects is matched by the variety of style, the quality is uniformly good. The end comes reluctantly; one wishes there were more. Dr. Watson of Baker Street does not appear, nor does Dr. Arrowsmith and there was apparently no room for that memorable picture

of medical student life to be found in "Of Human Bondage."

The authors are almost entirely modern. With three exceptions they are native to the English language and preponderantly American. Ernest Hemingway is the only writer with two selections in the book. Among others included are Conrad Aiken, Stephen Vincent Benet, Irvin S. Cobb, Pearl Buck, W. Somerset Maugham, Ring Lardner, Anton Chekhov, MacKinlay Kantor, Clarence Day, Jack London, A. J. Cronin, Erskine Caldwell, C. S. Forester and F. Scott Fitzgerald.

The volume is attractively bound and printed.<sup>5</sup>

F.K.H.

<sup>5</sup> A TREASURY OF DOCTOR STORIES BY THE WORLD'S GREAT AUTHORS. Edited by Noah D. Fabricant, M.D. and Heinz Werner. Cloth. Pp 500. New York, 1946. Frederick Fell, Inc. Price \$3.00.

## Editorial

### Streptomycin

**T**HERE is good evidence from the papers appearing in this symposium to support the statement that streptomycin is an extremely valuable anti-infective agent in the treatment of many infections that are resistant to either the sulfonamides or to penicillin. Thus, streptomycin has taken its place along with the sulfonamides and penicillin as a potent and valuable chemotherapeutic agent. Its effect in tularemia is unquestioned and in many cases dramatic. The results reported by Foshay are extremely impressive and carry great weight. The statement that "there is uniform agreement that streptomycin is an extremely effective therapeutic agent in tularemia" is supported by the data and by a wide experience with the treatment of this disease with other methods. It is noteworthy that highly satisfactory results can be obtained with a total dosage schedule of 2 to 3 Gm. given over a period of four to six days.

Dr. Alexander gives us precise information concerning the position of streptomycin in the treatment of *H. influenzae* meningitis. Her broad experience with the use of various methods of treatment in this disorder suggest that streptomycin should be used alone only in mild or moderately severe cases. The criteria for the use of various forms of combined therapy such as streptomycin alone, or sulfadiazine and antiserum, or the combined use of sulfadiazine with either streptomycin or Type B *H. influenzae*

antiserum are spelled out very clearly in the paper.

That streptomycin has a small but definite place in the treatment of bacterial endocarditis is emphasized by Hunter. The patients with gram-negative bacillary infections who have an organism that is sensitive to streptomycin should all receive treatment. Also, those patients with penicillin-resistant, streptomycin-sensitive organisms that fall into the gram-positive group should be treated intensively.

The position of streptomycin in the treatment of urinary tract infections has been defined by Hewitt and for wounds and peritonitis by Howes and Zintel, respectively. All these studies demonstrate that streptomycin plays a definite part in controlling these complicated infections.

The review of the present status of streptomycin treatment in tuberculosis by Hinshaw, Pyle and Feldman serves to stress once again the importance of studying this infection further and with greater intensity. One cannot help but be impressed with the positive effects of chemotherapy in these various tuberculous infections. When the statement that "streptomycin is the most effective antibacterial agent known for tuberculosis" is combined with another, "experience with this antibiotic agent has proved that tuberculosis is a disease amenable to antibacterial therapy," there are good grounds for believing that great strides will be made in developing new methods for



treating one of the most important infections in man.

The results reported by Finch in acute brucellosis strongly suggest that the treatment of these patients should be carried out over a period of at least three to four weeks with 2 to 3 Gm. of streptomycin a day. It is a striking fact that in this disease, as well as in enteric infections due to *E. typhosa* and salmonella strains, the results of treatment with streptomycin have not been dramatic or impressive. It is far from clear why typhoid bacilli that are sensitive to streptomycin *in vitro* cannot be destroyed in the body when concentrations of the antibiotic are obtained in body fluids that are higher than is necessary to kill the organisms *in vitro*. It would be of great importance if we knew the mechanism of this phenomenon.

It has been pointed out that one of the limiting factors in using streptomycin is the rapid development of so-called bacterial resistance. The mechanism by which this resistance develops is not wholly understood. Perhaps one of the reasons for our lack of understanding of this phenomenon is that we are almost wholly ignorant of the mode of action of streptomycin on bacteria. It is not too much to expect that more information concerning the mode of action of streptomycin might assist one in understanding this problem of bacterial resistance and provide us with ways and means of preventing its development.

The toxic reactions as summarized by

McDermott and the tests for bacterial sensitivity and methods of streptomycin determination in body fluids by Herrell and Heilman point to a number of the important practical features in the management of patients who are receiving streptomycin.

It seems plain from McDermott's studies that reactions from streptomycin follow the use of highly purified material as well as material containing not more than 50 to 60 per cent streptomycin. Also, it is clear that the larger the daily dose and the longer the treatment the higher the incidence of reactions. McDermott makes the point that toxicity cannot be considered apart from the diseases for which the drug is used. On a basis of his studies, it is stated that 3 Gm. a day represents the maximum limit of a safe dose. On the whole, however, it can be stated that the toxicity is sufficiently low to justify the use of this drug in all serious or potentially serious infections due to penicillin-resistant, streptomycin-sensitive organisms.

It can be said that streptomycin is another antibiotic agent that is extremely valuable and effective in controlling many infections that were uninfluenced by any other existing chemotherapeutic agent. Its discovery and application shows what can be accomplished in a group of extremely stubborn infections. It is to be hoped that our knowledge of its usefulness will be extended still further in the future.

CHESTER S. KEEFER, M.D.

# Streptomycin

## *General Considerations, Tests for Bacterial Sensitivity and Methods of Measurement of Streptomycin in Body Fluids*

WALLACE E. HERRELL, M.D.\* and FORDYCE R. HEILMAN, M.D.\*

ROCHESTER, MINNESOTA

THE antibiotic agent, streptomycin, was first described by Schatz, Bugie and Waksman<sup>1</sup> in January, 1944. The substance was produced by an actinomycete which had been discovered and described some years previously by Waksman. This actinomycete was subsequently placed in the genus *Streptomyces* by Waksman and Henrici<sup>2</sup> and is now known as "*Streptomyces griseus*." The newly discovered antibiotic was consequently given the name "streptomycin." Schatz, Bugie and Waksman suggested that this antibacterial agent possessed properties which might make it useful in the treatment of disease caused by certain gram-negative as well as some gram-positive pathogens.

Streptomycin behaves chemically as an organic base. It is rather thermostabile. It is not soluble in ether or chloroform but it is soluble in water and dilute acids. It was evident from the original reports that in the group of organisms which might be inhibited by the action of streptomycin were such microbes as *Escherichia coli*, *Bacillus subtilis*, *Aerobacter aerogenes*, *Proteus vulgaris* and some species of *Salmonella*. Likewise, it appeared that streptomycin possessed a limited suppressive effect on *Pseudomonas aeruginosa*.

That *Mycobacterium tuberculosis* was sensitive to the action of streptomycin *in vitro* was suggested by the reports by Waksman, Bugie and Schatz<sup>3</sup> and by Schatz and Waksman.<sup>4</sup> That streptomycin exerted an

inhibitory effect on *Mycobacterium tuberculosis in vivo* was first reported by Feldman and Hinshaw.<sup>5</sup> These and other studies led to a rather intensive experimental and clinical trial of streptomycin in the treatment of tuberculosis. The results of such studies will be discussed in other articles in the present symposium.

Further studies by the investigators at Rutgers University<sup>6</sup> revealed that streptomycin was effective in the treatment of certain experimental infections owing to *Salmonella schottmülleri*, *Pseudomonas aeruginosa*, fowl typhoid and *Brucella abortus*. Unfortunately, subsequent clinical trials have not proved streptomycin to be of outstanding value in the treatment of clinical infections due to the organisms just mentioned.

It was evident from the *in vitro* and *in vivo* studies reported by one of us (Heilman)<sup>7,8</sup> that streptomycin possessed therapeutic possibilities in the treatment of infections due to *Pasteurella tularensis* (tularemia) and infections due to organisms of the Friedländer group (*Klebsiella*). From studies carried out at the Mayo Clinic<sup>9</sup> and elsewhere<sup>10</sup> it was evident that streptomycin possessed antibacterial activity against *Hemophilus influenzae*. The studies reported by Hegarty, Thiele and Verwey<sup>11</sup> indicated likewise that streptomycin possessed value in the treatment of experimental infections owing to *Hemophilus pertussis*. While streptomycin has been used satisfactorily in the treatment of clinical cases of infection

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due to *Hemophilus influenzae*, studies on its possible use in pertussis have not been reported at the time of this writing.

Streptomycin has been found to inhibit the growth *in vitro* of a great number of microbes. In this article we are concerned only with those organisms which are considered pathogenic for man. The organisms which at present may be considered for practical purposes to be sensitive and which are pathogenic for man are listed in Table I. It should be emphasized, however, that

TABLE I  
ANTIBACTERIAL ACTION OF STREPTOMYCIN  
Organisms Sensitive to Streptomycin

<i>Escherichia coli</i>
<i>Eberthella typhosa</i>
<i>Salmonella paratyphi</i> (some strains)
<i>Salmonella enteritidis</i> (some strains)
<i>Shigella dysenteriae</i>
<i>Proteus vulgaris</i>
<i>Aerobacter aerogenes</i>
<i>Pseudomonas aeruginosa</i> ( <i>Bacillus pyocyaneus</i> )
<i>Klebsiella pneumoniae</i>
<i>Hemophilus influenzae</i>
<i>Hemophilus pertussis</i>
<i>Staphylococcus aureus</i> (some strains)
<i>Mycobacterium tuberculosis</i>
<i>Brucella melitensis</i>
<i>Brucella abortus</i>
<i>Brucella suis</i>
<i>Pasteurella tularensis</i>
<i>Pasteurella pestis</i>

the sensitivity of these organisms varies greatly. It should be emphasized further that the inclusion of an organism in this list does not mean that streptomycin has proved effective in the treatment of clinical infections due to that organism. For the purpose of the discussion the organisms might well be listed in two groups: (1) those that are rather highly sensitive and (2) those that are moderately sensitive. In the group of organisms which could be considered rather highly sensitive are placed *Pasteurella tularensis*, *Pasteurella pestis*, *Hemophilus influenzae*, *Hemophilus pertussis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus vulgaris* and *Mycobacterium tuberculosis*. The organisms which could be considered only moderately sensitive are *Eberthella typhosa*,

*Salmonella paratyphi* (some strains), *Salmonella enteritidis* (some strains), *Shigella dysenteriae*, *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), *Staphylococcus aureus* (some strains), *Brucella melitensis*, *Brucella abortus* and *Brucella suis*.

With certain exceptions, the sensitivity of organisms to streptomycin as determined by *in vitro* studies can be used as an index of the probable effectiveness of the antibiotic in treatment of clinical infections. It was evident from even the earliest experimental studies that the variation in sensitivity of different strains of the same organisms to the action of streptomycin was of considerable importance from a therapeutic point of view. Different strains of the same bacterial species may vary markedly in their sensitivity to streptomycin. This immediately suggests the importance of testing the sensitivity of the strain isolated from the patient before and during treatment. This necessitates a close collaboration between the clinician and the laboratory worker in the management of patients suffering from infections in which streptomycin may be used as a therapeutic agent.

Two other important considerations should be mentioned in connection with the therapeutic use of streptomycin. One is the definite variation in the absorption and excretion of streptomycin by different patients or by the same patient at different times. This variation may make the clinical evaluation of the antibiotic agent difficult at times. Second, but of no less importance, is the ability of certain pathogens to develop resistance to streptomycin. Some strains and species of organisms may develop resistance to streptomycin with incredible rapidity. This has been demonstrated repeatedly both *in vitro* and *in vivo*. This observation is exceedingly important from a clinical standpoint. Buggs and his associates<sup>12</sup> have pointed out, however, the difficulties which may be encountered in

studying this problem clinically. It is difficult at times to determine whether or not the same organism is being isolated at different times from a given patient. Moreover, organisms may develop resistance *in vitro* but will not necessarily develop resistance in the body. From a clinical standpoint it is important to remember that organisms which easily can be made resistant to streptomycin *in vitro* at times may retain their sensitivity in patients although the patient has received repeated courses of streptomycin.

All of the previously mentioned facts emphasize the importance of adequate laboratory methods of assay and adequate methods for testing bacterial sensitivity which will be discussed later in this paper. Furthermore, because of the reasons previously stated, certain dictums have been adopted in the clinical use of streptomycin. Because of the development of resistance, it is essential that bacteria be eradicated as completely as possible in the shortest possible time if good clinical results are to be obtained. This rule implies the administration of large doses of streptomycin from the onset of treatment. It also calls for frequent recourse to the laboratory for determination of the sensitivity of the organism especially if the infection is not responding satisfactorily to treatment. The removal of foreign bodies and the eradication of foci by surgical means before or soon after treatment is begun is important. The presence of foreign bodies or foci favors the continuation of infection and thereby favors the possibility of the development of resistance on the part of the infecting organism. In the treatment of infections in which stasis and obstruction play a rôle, such as in infections of the urinary tract, it is important that these two factors be eliminated. Since it is known that streptomycin exerts its maximal antibacterial effect in the presence of an alkaline medium, it is suggested that the urine should be kept alkaline.

Much has been learned concerning the absorption, diffusion and excretion of streptomycin. It was evident from the reports made by various investigators<sup>13-20</sup> that streptomycin, following its intramuscular or intravenous injection, diffuses rather readily into most body tissues. Following oral administration, streptomycin cannot be detected in significant amounts in the blood stream. On the other hand, the antibiotic is not destroyed in the gastrointestinal tract and large portions of the material administered orally can be recovered from the feces. It exerts an antibacterial effect on the intestinal flora and this observation suggests its use when a reduction in the bacterial content of the bowel is desired.

Satisfactory therapeutic concentrations of streptomycin will appear in the blood and urine following intermittent intravenous, intramuscular or subcutaneous administration. Approximately 60 to 80 per cent of streptomycin injected is excreted by the kidneys and may be recovered in the urine. It should be pointed out, however, that streptomycin at times may accumulate to toxic levels in the blood stream of patients who have poor renal function. Streptomycin appears to diffuse into the peritoneal cavity in substantial amounts in the presence of early peritonitis. Streptomycin does not diffuse readily into the cerebrospinal fluid of normal individuals; however, therapeutic amounts appear to diffuse readily into the spinal fluid in the presence of meningitis. Streptomycin diffuses into the tissues of the eye and also appears to diffuse through the placenta and thereby reaches the fetal circulation. It does not appear to diffuse readily into empyema cavities. Streptomycin appears to be excreted in the bile. When streptomycin is introduced into the tracheobronchial tree by means of nebulization, it is not absorbed into the blood stream in significant amounts.

When streptomycin was first introduced, the unit of potency was defined on the basis of its antibacterial activity. The unit of potency was based on that amount of the material required to inhibit the growth of a given strain of *Escherichia coli*. It was known as the "S" unit of Waksman. Recently, the metric system has been adopted in connection with dosage of streptomycin. One microgram of pure streptomycin is approximately equivalent to 1 S unit; 1 mg. to approximately 1,000 S units and 1 Gm. to 1,000,000 S units. Experience at present indicates that the minimal daily dose of streptomycin should be 1 to 3 Gm. (1,000,000 to 3,000,000 S units). In the treatment of overwhelming infection, as much as 5 Gm. per day may be given. For intermittent intravenous or intramuscular injections, the total daily dose is dissolved in 16 cc. of physiologic saline solution or distilled water. An average of 2 cc. of this solution is injected every three hours. In some instances, satisfactory results may be obtained by making larger injections at intervals of four or six hours. The recommended daily dose of streptomycin for oral administration is 2 to 4 Gm. in four divided doses. For intrathecal administration of streptomycin it is recommended that 100 mg. of streptomycin be dissolved in 5 or 10 cc. of physiologic saline solution. This quantity may be administered every twenty-four to forty-eight hours. For nebulization, the concentration recommended is, as a rule, 50 mg. per cc. of physiologic saline solution. For local application, concentrations of the drug which have been used vary from 10 to 100 mg. per cc.

#### CLINICAL TRIALS

In recent years streptomycin has been subjected to rather extensive clinical trials by a host of investigators. These trials have been limited, for the most part, to tuberculosis, bacteremia and subacute bacterial

endocarditis, peritonitis, influenzal meningitis, tularemia, infections of the urinary tract and undulant fever. Streptomycin also has been used locally in the treatment of wounds infected with organisms known to be sensitive to its action. A detailed discussion of these results will be dealt with in separate articles in this symposium. Some clinical experiences in the use of streptomycin in a variety of bacterial infections, treated at the Mayo Clinic have been reported elsewhere.<sup>21-25</sup>

#### TESTS FOR SENSITIVITY OF BACTERIA TO THE GROWTH-INHIBITING EFFECT OF STREPTOMYCIN

The activity of streptomycin in a bacteriologic medium is affected by the pH and by the presence of cysteine, sodium thioglycolate and other reducing substances.<sup>3,26-28</sup> In a medium highly favorable to bacterial growth more streptomycin may be required to inhibit growth of a given strain of bacteria than in a medium of deficient nutritional value.<sup>29,30</sup> Since streptomycin becomes less active if the substrate is acid or is in a reduced state, tests of sensitivity should be carried out in mediums containing no fermentable sugar and adjusted to a pH close to neutrality, and under aerobic conditions.

There are several methods of testing the sensitivity of bacteria to streptomycin. In one of these the test is carried out in a series of tubes, containing liquid medium suitable for growth of the organism, to which various amounts of the antibiotic<sup>12</sup> have been added. The liquid medium in the tubes is inoculated with a drop of a dilute suspension in broth of the organism and incubated for eighteen hours or until good growth appears in the control tube. The lowest concentration of streptomycin which completely inhibits growth is recorded. Since the end point of growth may be difficult to determine by inspection, a loopful of material from each

of the tubes near the end point may be streaked on an agar plate to determine in which tubes growth has or has not occurred. Prolonged incubation may allow the development of resistant forms and alter the end point. The larger the primary bacterial inoculum the greater the chance that it will contain some of the more resistant organisms which are usually present in any culture.

Because of the difficulty in determining the end point of growth in liquid mediums, in our laboratory tests for sensitivity to streptomycin are carried out routinely by streaking a dilute suspension of the organism on agar plates containing various amounts of streptomycin. The plates are prepared from nutrient agar adjusted to pH 7.2 to 7.4. Blood agar is used for more fastidious organisms. Seven plates are prepared in which have been incorporated by careful mixing, previous to solidification of the agar, 50, 25, 12.5, 6.25, 3.12, 1.56 and 0 units (micrograms) of streptomycin per cc., respectively. In order that several different strains of bacteria may be tested on one set of plates, each plate is divided into several sectors by marking on the back with a pencil used for marking glass. The sectors on each plate are numbered. Dilute suspensions in nutrient broth (which contains no sugar) of the organisms to be tested are prepared and a loopful of each suspension is streaked on each plate over the sector assigned to that suspension. A suspension of a stock strain of staphylococci of known sensitivity is always streaked on one of the sectors of each plate. The use of this stock strain is a test of the proper preparation of the plates and is of importance since the decision as to whether or not a patient is to be treated with streptomycin often rests on the results of this test of sensitivity. The inoculated plates are incubated at 37°C. overnight or until there is good growth of the test strain on the control plate containing no streptomycin. The lowest concentration of streptomycin which

completely inhibits growth of each strain then is recorded.

If the plate method is used, difficulty may be encountered in testing the sensitivity to streptomycin of freshly isolated strains of *Brucella abortus* which require an increased tension of carbon dioxide. Placing the plates in an atmosphere of 10 per cent carbon dioxide lessens the activity of streptomycin in the test plates, presumably by lowering the pH of the medium. After several subcultures, the carbon dioxide requirements of such strains are decreased sometimes. The organism then will grow in an atmosphere of 2 to 3 per cent carbon dioxide which concentration will not alter the pH of medium significantly and, therefore, will not alter the results of the test of sensitivity to streptomycin.

The standard solution of streptomycin used in making the dilutions for the preparation of the test plates is stable and may be kept in a refrigerator in a sterile corked tube for several weeks without significant loss of titer.

Simpler methods, giving less accurate measurements of the degree of sensitivity of an organism to streptomycin, are available. Plates seeded with the organism on which are placed cups filled with solutions containing various concentrations of streptomycin or disks of blotting paper (obtainable from Schleicher and Schuell, New York) dipped in such solutions may be prepared.<sup>31</sup> After incubation, inhibition of growth around the cups or disks is noted and compared with similar preparations on plates seeded with an organism of known sensitivity. Another method consists in dipping a disk of blotting paper in a solution containing 20 units of streptomycin per cc. and placing it on a plate of nutrient agar. Organisms to be tested are streaked outward from the periphery of the paper disk and the distance from the disk that growth is in-

hibited after incubation is an index of sensitivity.

#### MEASUREMENT OF STREPTOMYCIN IN BODY FLUIDS

Streptomycin in serum, urine or other body fluids is often measured by noting the volume of such material which must be added to a liquid bacteriologic medium to inhibit the growth of a test organism. It also frequently is measured by making various dilutions of the serum, placing these dilutions in cups on an agar medium inoculated with a test organism and after incubation measuring the zone of inhibition of growth around the cups.

Methods of making the test by adding various amounts of the serum or other fluid to be tested to liquid mediums containing the test organism have been described.<sup>15,32,33</sup> Such methods are somewhat more sensitive than the cup-plate method and simpler to perform. Their disadvantages are that the body fluid to be tested must be sterile; the end point of growth in liquid mediums is often difficult to determine; different amounts of body fluid may have different growth promoting properties for the test organism, and end points between the dilution intervals used cannot be detected.

In our laboratory, a method of using cups on agar plates which is similar in principle to that described by Stebbins and Robinson<sup>34</sup> is favored. This method does not accurately measure concentrations of streptomycin of less than 1 unit per cc. but since weaker concentrations are of doubtful therapeutic effectiveness, the method is sufficiently sensitive for general use. The test organism is a strain of *Staphylococcus aureus* which on agar gives relatively sharp margins at the edges of the zones of inhibition.

The test organism is maintained in nutrient broth by daily transfer. Since growth of the organism for prolonged periods on broth has yielded variants which have lessened

the sharpness of the edges of zones of inhibition around the cups, the series of cultures in broth is discarded at the end of a week and a new series is started from a stock agar slant culture which is preserved in the refrigerator.

The test is carried out in a system adjusted to pH 8. This pH is chosen because streptomycin is more active at pH 8 than at neutrality. All dilutions in the test are made in a sterile tenth-molar pH 8 buffer, prepared from potassium phosphate ( $\text{KH}_2\text{PO}_4$  and  $\text{K}_2\text{HPO}_4$ ). Nutrient agar adjusted to pH 8 is used as the test medium. A commercial dehydrated medium with the pH already adjusted and known as "Streptomycin Assay Agar" (Difco) is satisfactory for the purpose. To furnish a perfectly flat surface for the test 12 cc. of unseeded melted agar is placed in each of a series of Petri dishes and allowed to harden. A second portion of melted agar is cooled carefully in warm water to 44° to 45°C. and inoculated with a broth culture of staphylococci which has been incubated for six hours. One cc. of a 1 in 100 dilution of this broth culture in a buffer solution is used for each 9 cc. of agar. A final dilution of  $10^{-3}$  of the staphylococcal culture is obtained. The inoculated agar is agitated to distribute the organisms evenly. With a warm, widemouthed pipette 5 cc. of the seeded agar is distributed over the surface of the first layer of agar on each plate while the plate is rotated so that the seeded agar forms an even layer.

Sterile beveled porcelain or glass cylinders, such as are used in the assay of penicillin (sold under the trade name of penicylinders), are warmed slightly in a flame and placed on the surface of the hardened agar. These cylinders should be just warm enough to seal the beveled surface in the agar. Four or five sterile cylinders are placed on each plate. Four or more serial 1:1 dilutions in buffer of the samples of body fluids for assay are prepared, the

number of dilutions depending on the expected concentration of streptomycin. For the standard, dilutions of streptomycin in buffer are prepared which contain 1, 2, 3 and 4 units per cc., respectively. Each of the dilutions of the test sample and standard is placed in a separate cup with a capillary pipette; each cup is nearly filled. Duplicate tests are set up on a separate set of plates for all of the samples as well as the standard. The Petri dishes are covered with unglazed porcelain tops to prevent dripping from condensed water and placed in the refrigerator overnight to allow the material to diffuse from the cups into the agar. Following this the plates are incubated for twenty-four hours at 30°C. Then the cups are removed from the plates and the diameter of the zones of inhibition of growth of the staphylococci is estimated to the nearest 0.2 mm., preferably by means of a colony counter equipped with a glass plate ruled 10 lines to the centimeter. Such ruled glass plates are available from commercial sources.

The diameters of the zones from duplicate cups are averaged. A curve is drawn on arithmetic graph paper by plotting the diameter of the zones of inhibition of the cups containing the standard streptomycin solutions on the ordinate against the concentrations in units of streptomycin per cc. of fluid on the abscissa. For a model, one of several references may be consulted.<sup>35-37</sup> From the standard curve the concentration of the drug in the sample under test can be read by noting the concentration of streptomycin on the abscissa of the standard curve which corresponds on the ordinate to the diameter of the zone of inhibition around the samples. This reading should be multiplied by the dilution of the body fluid used in the cups. If sizes of the zones of two different dilutions of the sample fall within the range of the standard curve, the concentration of each dilution is calculated and the results

are averaged to give the concentration in the body fluid.

Specimens contaminated with bacteria may be assayed by this method. Two cc. of a sample is required for an assay. With assays of urine, if it is desired to hurry the test, the plates may be placed directly in the incubator without preliminary storage in the refrigerator since urine diffuses rapidly from the cups. Samples of the original specimen being assayed should be preserved in the cold in case the assay has to be repeated at higher dilutions. Disks of blotting paper dipped in the test fluid or measured drops of test fluid placed directly on the seeded agar are used in place of cups by some workers.<sup>36,37</sup>

If only an estimate of the amount of streptomycin is desired, the test may be simplified. Several cups placed on a plate of seeded agar are filled with various dilutions in saline solution of the sample to be tested and the plates are incubated at 30° or 37°C. overnight. The extent of the zones of inhibition is a rough measure of the concentration of streptomycin.

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# Streptomycin in Tuberculosis<sup>\*</sup>

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ALTHOUGH attempts to attack tuberculosis by chemotherapeutic means are as old as our knowledge of the disease, it was not until 1940 that a substance was found capable of arresting tuberculosis *in vivo*. In that year Feldman, Hinshaw and Moses<sup>1</sup> reported that promin (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) had a striking effect on tuberculosis induced in guinea pigs. A few other drugs of the sulfone series were found to have a similar suppressive effect on experimental tuberculosis, and attempts to use these drugs clinically followed.<sup>2</sup> The results were suggestive but never fully convincing, possibly because the sulfone compounds were found to be too toxic to permit adequate treatment of tuberculosis of human beings.

From the first, streptomycin gave great promise as an agent capable of suppressing tuberculosis. In their early reports Schatz and Waksman<sup>3</sup> noted that a human strain of *Mycobacterium tuberculosis* was sensitive to streptomycin *in vitro*. Investigations of this antibiotic agent were begun in April, 1944, at the Mayo Foundation with the methods previously developed for chemotherapeutic testing in experimental tuberculosis.<sup>4</sup> These investigations proved conclusively that streptomycin consistently would arrest and at times even apparently eradicate well established tuberculosis in the highly susceptible guinea pig.<sup>5,6</sup>

In the most severely controlled of the experiments, forty-nine guinea pigs were infected with a virulent standard human

strain of tubercle bacilli. Forty-two days later results of tuberculin tests of all the animals were positive. On the forty-eighth day of infection biopsy of the liver was performed in each case and histologic evidence of the disease was obtained. On the forty-ninth day after infection twenty-five of the animals were treated with streptomycin. Treatment was continued for a total of 166 days. Approximately 70 per cent of the control animals succumbed to infection within this period, whereas only 8 per cent of the animals treated died before the experiment was terminated 215 days after infection.

At necropsy all control animals showed evidence of severe, widely disseminated tuberculosis. In marked contrast, the treated animals showed little or no gross or microscopic evidence of infection. In a majority of animals, treatment with streptomycin must have had a suppressive rather than a sterilizing effect on the infection, because tubercle bacilli were recovered by animal inoculation tests from the spleens of fifteen of the twenty-five treated animals. However, in nine of the treated animals the sensitivity to tuberculin was reversed from positive to negative, and in only two of this group were tubercle bacilli recovered from the spleens by animal inoculation. Streptomycin was tolerated well by the test animals, and there was no histologic evidence of drug toxicity in any of the organs. Youmans and McCarter<sup>7</sup> reported equally encouraging results from the treatment with strepto-

<sup>\*</sup> From the Mayo Clinic, Rochester, Minnesota.

mycin of mice infected experimentally with tuberculosis.

#### CLINICAL USE OF STREPTOMYCIN\*

The clinical use of streptomycin for tuberculosis was begun in December, 1944. In the last two years streptomycin has been used by our colleagues and us in more than 100 cases of tuberculosis of various types. A preliminary report of the earlier work was given in September, 1945,<sup>8</sup> and more recently a more comprehensive account was published in collaboration with Dr. Karl H. Pfuetze.<sup>9</sup> At present approximately 200 additional patients are being treated with streptomycin at selected institutions, under the auspices of the American Trudeau Society. In addition, a large number of patients are receiving streptomycin for tuberculosis in other institutions. When the mass of data from all this investigation is assembled, perhaps within a few months, it should be possible to make a more accurate appraisal of the drug, not only in regard to its therapeutic efficacy in tuberculosis, but also as to its toxicity and such factors as the effective dosage and optimal duration of treatment.

In all discussions of the therapeutic possibilities of streptomycin in tuberculosis, we must view the situation in proper perspective. The ability of streptomycin to suppress the disease is unique and at times apparently remarkable. The limitations of streptomycin are just as real. Because of certain toxic potentialities, its inadequacy in some clinical situations, and the expense of prolonged periods of treatment, the indiscriminate use of streptomycin in the treatment of tuberculosis must be discouraged.

\* The streptomycin used in these studies was supplied by Merck & Co., Inc., Abbott Laboratories, and The Upjohn Company. From March 1 to September 1, 1946, all supplies were allocated through the Committee on Chemotherapeutics and Other Agents of the National Research Council, Dr. Chester S. Keefer, Chairman. Since September, 1946, material has been supplied by the Committee on Therapy of the American Trudeau Society.

Among the indications for the use of streptomycin in tuberculosis are all forms of hematogenic disease, including generalized miliary tuberculosis and meningitis, the prognosis of which has hitherto been regarded as hopeless. Of twelve patients who had disease of this type and were treated with streptomycin at the Mayo Clinic, four are still living and have been observed for periods of from six to twelve months. Treatment of each of these four patients has been discontinued for from four to six months, and there is not any evidence of reactivation of the disease. Three of these patients who originally presented the classic picture of tuberculous meningitis, are ambulatory and free of symptoms, although two of them have residual neurologic disturbances. One of these two has marked nerve deafness which may be a toxic effect of streptomycin. The other patient has symptoms of cerebellar dysfunction, which are thought to be sequelae of the meningitis.

In treating tuberculous meningitis it is imperative that streptomycin be given both parenterally and intrathecally and as early in the course of the disease as possible. The first five patients who were given streptomycin for tuberculous meningitis at the Mayo Clinic received it parenterally only. Although four of them improved temporarily, all eventually died.<sup>10</sup> It is suggested that the drug be given by lumbar or cisternal puncture, in amounts of from 100 to 200 mg. every twenty-four to forty-eight hours for from four to seven weeks or longer. A single dose of streptomycin is dissolved in 8 to 10 ml. of physiologic saline solution and injected after the withdrawal of 10 to 15 ml. of spinal fluid. In addition, streptomycin probably should be given parenterally for a long period. The four patients with tuberculous meningitis who survived received an average dose of 2 Gm. a day by parenteral administration for an uninterrupted period of six months.

The patient who has early tuberculous meningitis usually improves in all respects within one to three weeks after treatment with streptomycin is begun. In our more successful cases it has been impossible to demonstrate tubercle bacilli in the spinal fluid, either by culture or inoculation of guinea pigs, after six to eight weeks of treatment, although their presence was demonstrated prior to treatment in each case. There is a tendency for the spinal fluid to remain somewhat abnormal; for example, the cell count and the concentration of protein are usually higher than normal.

Generalized miliary tuberculosis, likewise, should be treated vigorously; the patient should receive 2 to 3 Gm. of streptomycin daily by parenteral administration for several months. Striking, often almost complete clearing of the pulmonary lesion is noted in the roentgenograms within a month or two, but if actual healing is to occur, treatment must be prolonged. One patient in our group who had generalized miliary tuberculosis without meningitis received 2.4 Gm. of streptomycin a day for a period of four months. His disease has remained in a state of clinical remission for three months since cessation of treatment. Treatment in three similar but more advanced cases of miliary tuberculosis resulted in temporary improvement only.

In addition to pulmonary lesions of hematogenic origin, pulmonary tuberculosis suitable for treatment with streptomycin includes recent lesions of bronchiogenic dissemination, exudative lesions, and in general all recent but rapidly progressive tuberculosis which is not likely to be brought under control by the usual methods of treatment. Pulmonary tuberculosis has been treated satisfactorily by average daily doses of from 1 to 3 Gm., administered parenterally, for a total period of from two to six months. Clinical improvement, including decrease in fever, increase in appetite and

reduction in cough and expectoration, is noted early, often within a week or two after administration of streptomycin is begun. Improvement usually can be demonstrated roentgenographically within one to two months. Although closure of pulmonary cavities has been observed roentgenographically during the period of treatment with streptomycin or in the ensuing months, cavities more frequently remain patent, especially if they are thick walled. Likewise the findings in the sputum are changed from positive to negative in only approximately 50 per cent of cases of far advanced pulmonary tuberculosis with extensive cavitation.

In our experience the patient whose pulmonary tuberculosis has improved during treatment with streptomycin usually continues to improve after this treatment is discontinued. In only a few cases of pulmonary tuberculosis has reactivation or extension of the disease occurred after cessation of treatment. If the tubercle bacilli recovered from the sputum of these patients are still sensitive to streptomycin *in vitro*, it is likely that the patient will respond to further treatment with the drug. If the strain has become resistant, there is less likelihood of repeating the earlier therapeutic result; but in some instances it has appeared that the resistant strains of bacilli were in the sputum and clinically sensitive strains were in the recurrent lesions.

Use of streptomycin in pulmonary tuberculosis possibly is indicated in conjunction with surgical procedures, such as lobectomy, pneumonectomy and even thoracoplasty. It is hoped that a preoperative course of the drug for one to three weeks and a postoperative course for two to four weeks will improve the patient's condition for operation and decrease the incidence of complications, such as the recrudescence of foci, extension of the disease to new regions and the development of tuberculous empyema. It is reasonable to believe that streptomycin

may make surgical intervention feasible more frequently in the treatment of tuberculosis.

A category in which streptomycin has been used with notable success includes tuberculosis of the hypopharynx, larynx and tracheobronchial tree. In our series of ten cases of tuberculosis in these sites lesions have healed promptly and have shown no tendency to recurrence for as long as twenty months after completion of treatment. For these ulcerating lesions of the respiratory tract we have given streptomycin both parenterally and by means of nebulization. For nebulization 500 mg. of streptomycin is dissolved in 20 ml. of physiologic saline solution and the patient is instructed to nebulize 2 ml. every hour for ten hours of the day. Repeated bronchoscopic examinations usually have revealed that healing was beginning within two weeks after treatment was started, and often healing was complete within four weeks. Treatment should probably be continued for seven or eight weeks or longer. It has not yet been determined whether either nebulization of streptomycin or its parenteral administration would be sufficient without the other method of treatment.

In our experience tuberculous draining sinuses have responded well to treatment with streptomycin, even those of long duration which were refractory to all other methods of treatment. These include fistulous tracts due to tuberculosis of the chest wall, abdominal wall and scrotum, and to tuberculous lymphadenitis. We have learned that to prevent recurrence of these conditions it is necessary to continue treatment for several weeks after drainage has ceased, with superficial healing. Streptomycin is given parenterally, and adequate treatment apparently consists of about 2 Gm. a day for three or four months.

Other forms of tuberculosis in which encouraging results have been obtained with

streptomycin therapy in small series of cases include tuberculosis of the alimentary tract and peritoneum and tuberculosis of bones and joints. Results have been excellent in one case of previously intractable lupus vulgaris. In some other cases presumed to be cutaneous tuberculosis, improvement from treatment with streptomycin has been temporary or questionable.

Streptomycin has been somewhat disappointing in the treatment of some cases of tuberculosis of the genitourinary tract. As has been reported previously,<sup>11</sup> marked symptomatic improvement occurs in more than 50 per cent of such cases and the degree of tuberculous bacilluria usually is reduced sharply. In fact in several cases in which we and the urologists at the clinic collaborated in the treatment, the urine became free of *Mycobacterium tuberculosis*, as proved by culture and inoculation of guinea pigs. However, the tendency of tuberculous lesions in the kidney of human beings not to heal is well known and, therefore, the benefits of antibacterial treatment are often only temporary. After weeks or months of treatment or at varying intervals after treatment is discontinued, the tuberculous bacilluria is likely to return. The strain of tubercle bacilli is then usually resistant to streptomycin *in vitro*. It may be worthy of note that some patients continue to have amelioration of their symptoms, even after a resistant strain of *Mycobacterium tuberculosis* appears in the urine. Because of the palliative effect, the possibility of arresting the disease in a small proportion of cases, and the inadequacy of other therapeutic measures, streptomycin is certainly worthy of trial in some cases of bilateral renal tuberculosis and in tuberculosis of a solitary kidney. We do not regard it as a substitute for surgical procedures in cases of unilateral renal tuberculosis, although it may yet prove to be of value in the preoperative and postoperative treatment.

Among tuberculous conditions in which streptomycin is not indicated or in which the indication is less definite, we include all cases in which satisfactory progress is made on a regimen consisting of the usual therapeutic measures. This category would include most cases of minimal pulmonary tuberculosis. Although sometimes lesions in such cases heal exceedingly slowly, it is generally agreed that most minimal lesions in the lung will undergo spontaneous regression or become arrested under favorable conditions. In the few cases of minimal pulmonary lesions in which streptomycin has been used, it would be difficult to prove that streptomycin accelerated the healing process. Inasmuch as the toxicity of streptomycin is being treated as a separate subject in this symposium, it will not be discussed here except to say that the potential toxicity appears to be sufficient to deny the drug to patients who can make a satisfactory recovery without it. The danger is not sufficient to justify denying streptomycin to any patient who is likely to obtain appreciable gains from such treatment.

At present we do not consider chronic fibrocaceous pulmonary tuberculosis suitable for treatment with streptomycin unless there is a conspicuous component of more recent exudative disease. Also, our experience has indicated that it is useless to expect streptomycin to be effective in obviously terminal cases of destructive types of pulmonary tuberculosis.

Tuberculous empyema is another condition in which treatment with streptomycin has been disappointing, whether the drug is administered parenterally, intrapleurally or by both methods. Possibly this is due to the fact that purulent empyema fluid is usually frankly acid in reaction, whereas streptomycin is more effective in an alkaline solution. In our series of seven cases, treatment was truly successful in only one case.

This patient had tuberculous empyema complicated by a bronchopleural fistula and several draining sinuses of the chest wall. She had been under our observation for four years, in the course of which she had undergone several surgical procedures without any improvement in her condition. She received 1.2 Gm. of streptomycin daily, and in addition a 1 per cent solution of the drug in physiologic saline solution was sprayed into the empyema cavity several times a day. The bronchopleural fistula closed within three weeks, the chest wall healed soon afterward, and it was impossible to recover *Mycobacterium tuberculosis* from the pleural fluid after three months of treatment. At present, ten months after cessation of treatment with streptomycin, the infection has not recurred. When tuberculous empyema is refractory to other methods of treatment, a trial of streptomycin may be worth while. It will be interesting to note the experience of other investigators who may be able to improve on our methods of employing streptomycin in cases of tuberculous empyema.

It must always be emphasized that treatment with streptomycin is not a substitute for rest in bed and sanatorium care, which are still fundamental in the treatment of tuberculosis. Nor can it be expected to supersede collapse therapy and other surgical procedures when these are indicated.

#### REASONS FOR LIMITATIONS OF TREATMENT WITH STREPTOMYCIN

The limitations of treatment with streptomycin are due to several factors probably inherent in any form of antibacterial therapy for tuberculosis. In the first place, the tissue changes in this disease tend to be destructive and proliferative. Older lesions, especially, are relatively avascular and, therefore, difficult of access for a blood-borne antibacterial substance.

In the second place, streptomycin is predominantly bacteriostatic rather than bactericidal. Youmans<sup>12</sup> found that of a total of fifty-eight human and bovine strains of tubercle bacilli, the growth of 70.8 per cent was inhibited by less than 1 microgram of streptomycin per milliliter of media. On the other hand, a concentration of more than 50 micrograms per milliliter was necessary to produce a bactericidal effect on the tubercle bacillus. The behavior of the drug *in vivo* seems to parallel its activity *in vitro*. The bacteriostatic action produces a limited suppressive effect on the disease and allows the patient to muster his natural defense forces. If these are sufficient and if the disease process is essentially curable, the ultimate result of treatment with streptomycin probably will be good.

In the third place, the therapeutic potentialities of streptomycin are limited because the duration of bacteriostatic action is limited. After prolonged exposure to streptomycin, strains of *Mycobacterium tuberculosis* may be isolated which are several thousand times as resistant to the effects of the drug as those isolated originally. This problem of drug fastness appears to be paramount at present. The relation of dosage to the factor of resistance has not been determined, but apparently a dose as large as 3 Gm. a day will not prevent its occurrence. Fortunately, the tubercle bacillus multiplies at a leisurely rate, so that resistance to an antibacterial agent does not become a problem so soon as in the case of other bacteria. From data available at present, the period from the beginning of treatment to the appearance of resistant strains varies from one to several months. Sometimes a resistant strain of *Mycobacterium tuberculosis* may be recovered from a patient and subsequently strains sensitive to streptomycin may be recovered following cessation of treatment. Patients may benefit

from a second course of treatment with streptomycin for recurrent tuberculosis. Whether the problem of resistance to streptomycin can be circumvented remains to be seen. A second antibacterial agent is now being used in conjunction with streptomycin in hope of retarding or preventing development of resistant strains. Variations in dosage schedule are also being employed.

#### SUMMARY

Streptomycin is the most effective antibacterial agent known for tuberculosis. *In vitro* it has a marked bacteriostatic action on the tubercle bacillus, and *in vivo* it tends to exert a deterrent effect on the disease in both animals and man. Its therapeutic value is limited by the fact that after exposure to streptomycin for weeks or months, strains of *Mycobacterium tuberculosis* which are resistant to the effects of the drug may be isolated. Hence streptomycin is of most value in conditions in which temporary suppression of the infection will enable the patient to gain the ascendancy over his disease; healing then occurs by natural processes.

Prolonged arrest of the disease has been achieved by treatment with streptomycin even in cases of hematogenic tuberculosis, including generalized miliary tuberculosis and tuberculous meningitis. For these conditions large doses of streptomycin must be given parenterally for several months, and for meningitis intrathecal injections are imperative also during the early weeks of treatment. Other types of tuberculosis which have responded to treatment with streptomycin include exudative pulmonary disease, ulcerating lesions of the respiratory tract and tuberculous draining sinuses. It has some place in the treatment of bilateral renal tuberculosis or tuberculosis of a solitary kidney. It also is used before and after thoracic surgery for pulmonary tuberculosis. Because of the potential toxicity,

use of the drug probably is contraindicated in conditions which will respond satisfactorily to the usual methods of treatment.

Our knowledge of streptomycin is still in a state of flux. Now that the drug is undergoing extensive clinical investigation in many institutions its ultimate place in the treatment of tuberculosis will be determined in time. Experience with this antibiotic agent has proved that tuberculosis is a disease amenable to antibacterial therapy and it is hoped that other usable agents will be forthcoming.

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# Use of Streptomycin in the Treatment of Bacterial Endocarditis\*

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**F**EW reports<sup>1,2</sup> have appeared concerning the treatment of bacterial endocarditis with streptomycin. Since the great majority of cases are caused by streptococci which are sensitive to penicillin and can be cured by this drug, only occasional cases require other forms of therapy.

The first and most obvious cases in which streptomycin seems to be the drug of choice are those in which the causative agent is a streptomycin-sensitive gram-negative bacillus. These organisms are almost without exception unaffected by penicillin, and many of them exhibit high resistance to sulfonamides. Furthermore, the latter drugs have been shown<sup>3</sup> to diffuse poorly into fibrin and probably do not reach the depths of vegetations readily.

The second category of bacterial endocarditis in which streptomycin therapy must be considered consists of the small fraction, perhaps 10 per cent, of cases of non-hemolytic streptococcus endocarditis in which the organism is resistant to penicillin from the start plus the still smaller fraction whose organism becomes resistant during penicillin therapy.

Six cases falling in one or another of these categories have been treated with streptomycin at the Presbyterian Hospital. One of these has already been reported.<sup>2</sup> This patient, with classical bacterial endocarditis due to an unidentified gram-negative bacil-

lus, was treated with streptomycin, 3 Gm. a day for ten days following an eighteen-day course of sulfadiazine. He has now been followed for seventeen months without clinical or bacteriological evidence of relapse. Brief summaries of the remaining five cases are presented.

## CASE REPORTS

CASE II. J. B., a fifty-seven year old male, with no history of previous heart disease, was admitted to the urological service of the Presbyterian Hospital in January, 1946, because of an infected diverticulum of the urinary bladder which was excised on February 8, 1946. Following the operation he developed a swinging fever and *B. pyocyaneus* was repeatedly grown both from the wound and from the blood cultures. The course was uninfluenced by sulfadiazine and under observation he developed a harsh apical systolic murmur. The organism required 15 micrograms of streptomycin for inhibition *in vitro* throughout. Streptomycin, 3 Gm. a day, 0.5 Gm. every four hours intramuscularly, was started on February 21st and continued for fourteen days following which the dosage was increased to 4 Gm. a day for five more days. The patient improved clinically and, after the first week of therapy blood cultures were sterile, but he continued to have lowgrade fever. The day after streptomycin was stopped the temperature again rose to 103° F. and blood culture was positive. On March 15th, therapy was resumed, this time with 6 Gm. of streptomycin a day, and was continued for seven days, but fur-

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The streptomycin was provided in part by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

ther treatment was not considered advisable since blood cultures continued positive in the face of such large doses of the drug. The patient died on April 22nd and at autopsy was found to have a large friable vegetation on an otherwise normal mitral valve.

CASE III. T. P., a fifty-one year old Italian barber, was admitted to the Presbyterian Hospital in August, 1946, with a six months' story of weight loss, night sweats and easy fatigability. Though there was no history of rheumatic fever, he had the murmurs of mitral valvular disease. In addition, there were low-grade fever, clubbing of the fingers, and a palpable spleen. At first the diagnosis was in doubt and a complete workup for fever of unknown origin was essentially negative until finally a gram-negative bacillus grew out in several blood cultures. The organism has not been positively identified, but is not one of the commonly encountered groups. It grew so slowly that *in vitro* tests of sensitivity were of doubtful value, but it was inhibited by 1 or 2 micrograms of streptomycin, whereas cultures had been positive while the patient was receiving 1,600,000 units of penicillin daily and the organism appeared to be resistant to this drug. Accordingly, he was started on streptomycin, 3 Gm. daily, 0.5 Gm. every four hours intramuscularly, and this was continued for three weeks during which time his temperature fell to normal, the blood cultures became sterile and have remained so to the present, two months after cessation of therapy. On the eighteenth day of therapy dizziness and unsteadiness of gait appeared. Vestibular tests showed a complete loss of response at this time, but audiograms showed no change. Since he showed some evidence of spinocerebellar involvement as well, a lumbar puncture was done, revealing normal findings except for a spinal fluid protein of 80 mg. per cent. The patient's subsequent course has been marked by slow subjective improvement in the unsteadiness, with loss of all vertigo. Spinal fluid examination was repeated two weeks later and again showed a protein of 75 mg. per cent. The explanation for this spinal fluid abnormality is not clear, but it occurred at a time when the patient had no signs of uncontrolled infection and was not having evident

embolic phenomena. Whether or not it is connected with toxicity of streptomycin remains obscure.

CASE IV. H. E., a forty-nine year old negro male, was admitted to the Presbyterian Hospital in March, 1945. Although he had no history of rheumatic fever there was a harsh apical systolic murmur and he had had fever and malaise for four months. Blood cultures had repeatedly grown a hemolytic streptococcus at another hospital where he had received penicillin, 200,000 units a day, plus sulfapyridine without even temporary sterilization of the blood stream. The organism recovered at this hospital proved to be a hemolytic streptococcus of the Lancefield group D which required 3 units per cc. of penicillin or 8 micrograms per cc. of streptomycin for inhibition of growth *in vitro*. During the next three months he received three courses of penicillin by constant intramuscular and intravenous drip consisting of 5,000,000 units a day for twelve days, then 10,000,000 units a day for fourteen days on two occasions. In each instance the blood cultures were sterile during therapy but became positive within four or five days of stopping. Finally, in August, 1945, he was given streptomycin, 3 Gm. a day, by constant intravenous and intramuscular drip for fourteen days. Daily blood levels of streptomycin averaged 51 micrograms per cc. varying between extremes of 22 and 96. Blood cultures remained sterile during therapy and for four days after but on the seventh day were again positive. No further treatment was attempted because the patient's general condition had deteriorated badly by this time. He was transferred to another hospital where he died six weeks later. No autopsy was performed.

CASE V. I. H., a twenty-six year old nurse, with known mitral disease, was admitted to the Presbyterian Hospital in February, 1946, with an eight months' story of chills, fever, embolic phenomena and weight loss. The diagnosis of bacterial endocarditis had been established by repeated positive blood cultures at another hospital where she had been given intensive penicillin treatment over a period of two months with daily doses up to 2,200,000 units a day. In spite of this, blood cultures had been positive throughout. The organism proved to be a

*Streptococcus fecalis* of Lancefield group D which required 8 units of penicillin and 3.5 micrograms of streptomycin *in vitro* for inhibition. Since the organism appeared to be more susceptible *in vitro* to a combination of the two antibiotics than to either alone, it was decided to give the patient 4 Gm. of streptomycin plus 4,000,000 units of penicillin a day for four weeks. At first the drugs were combined in a single infusion of saline but on the sixth day, the patient's temperature spiked to 105° F. and it was noted that there was a precipitate in the flask. Subsequently, penicillin was given by constant drip, either intravenous or intramuscular, and streptomycin was injected intramuscularly every three hours. In the third week, she complained of transitory dizziness on two occasions when out of bed but otherwise her course was one of steady improvement. Blood cultures have all been sterile since therapy began. She has now been followed for ten months post-therapy and is leading a normal life free from evidence of infection. She has complained of slight unsteadiness of gait especially in the dark which has slowly improved. Unfortunately, it has not been possible to get tests of vestibular function, but it seems likely that these symptoms represent the toxic effect of streptomycin.

CASE VI. E. H., a sixty-eight year old male, was admitted to the Presbyterian Hospital in October, 1946, with a diagnosis of bacterial endocarditis of three months' duration. There was no history of rheumatic fever but he showed the signs of mitral disease without evidence of cardiac failure. Blood cultures had been repeatedly positive at another hospital and a *Streptococcus viridans* persisted in the blood stream during therapy with 100,000 units of penicillin every three hours. The organism proved to be an enterococcus of Lancefield group D requiring 1.0 unit of penicillin or 20 micrograms of streptomycin for inhibition of growth *in vitro*. He was first given 700,000 units of penicillin every three hours intramuscularly (5,600,000 units daily) for three weeks during which time blood cultures were sterile and the patient clinically improved. Cultures became positive again one week later, the organism now requiring 1.0 unit of penicillin or 30 micrograms of streptomycin for inhibition. He was next

given 20,000,000 units of penicillin daily for sixteen days and again there was clinical improvement. Blood cultures were sterile during therapy and penicillin serum levels reached as high as 100 units per cc. Two weeks after this course the patient continued afebrile and felt well, but blood cultures again were positive, the organism now requiring 10 units of penicillin or 40 micrograms of streptomycin for *in vitro* inhibition. Although it seemed unlikely that streptomycin would be effective, it was then administered in doses of 6 gm. daily, but since blood cultures continued positive in the face of therapy, it was abandoned after one week. The course subsequently was slowly downhill in spite of a trial on bacitracin and blood cultures were persistently positive. Organisms recovered from the blood after streptomycin administration required more than 100 micrograms of the drug for inhibition of growth *in vitro*. At autopsy a large vegetation was present on the mitral valve; microscopic findings have not yet been reported.

In summary, of our three cases due to gram-negative organisms, treatment with streptomycin appears to have effected cure in two patients and failed in one instance. Of the three patients infected with penicillin-resistant streptococci, only one responded to streptomycin and this patient received large doses of penicillin in conjunction.

Dr. Chester S. Keefer has kindly supplied us with reports on twelve additional cases treated at various clinics throughout the country under the program for clinical trial of streptomycin (Cases 7-18, Table 1). Five patients had endocarditis due to various types of gram-negative bacilli. Of these three were definite failures, one patient with *H. influenzae* endocarditis was probably cured on streptomycin in combination with sulfadiazine, and one patient with infection due to an unidentified microaerophilic gram-negative bacillus appears to be well after a course of penicillin followed by streptomycin. The exact rôle of strepto-

mycin in the last two cases cannot be definitely determined, but it probably contributed to the favorable results.

In the remaining seven patients, the causative organisms were gram-positive cocci. One patient, with a staphylococcal endocarditis due to an organism which was penicillin-resistant but sensitive to 0.4 microgram of streptomycin, was apparently cured after a course of 1.5 to 3 Gm. daily for twenty-eight days. Of four patients harboring a penicillin-resistant *Streptococcus viridans*, two appear to be cured. One patient's organism was sensitive to 5 micrograms of streptomycin *in vitro*, and he received 3 Gm. daily for thirty-four days. The second patient received 3.0 Gm. the first day followed by 1.0 Gm. daily for fifteen days; the *in vitro* sensitivity in this patient is not recorded.

The two remaining patients had infections caused by enterococci. In one temporary sterilization of the blood stream was obtained, but the patient had a recurrence of infection three months later. On subsequent treatment, the infection persisted and culminated in death in spite of the administration of doses up to 8 Gm. of streptomycin per day. In this case during the second course of streptomycin, the organism at the beginning was reported as sensitive to 0.2 micrograms of the drug, but later is said to have required seventy-five times as much by *in vitro* test. The second case of enterococcus infection failed to respond to therapy though 3 Gm. daily were administered in two courses of two weeks each. Data on sensitivity of the organisms are not available.

Combining the figures on all cases reported, of eighteen cases treated probable cure has been the result in eight. The rôle of streptomycin is open to some question in four of these eight. The remaining ten cases were definite failures at the dosages employed.

It will be noted in Table 1 that seven patients showed the common toxic manifestations of streptomycin due to vestibular damage, and that there is a rough correlation with total dosage and duration of therapy. It is probable that other cases would have shown damage to the eighth nerve had routine function tests been employed. In only two patients was there definite evidence of decreased auditory acuity. In one of these (Case 12) it may be significant that there was renal damage with nitrogen retention at the beginning of therapy. The other (Case 7) may not be attributable to streptomycin, as symptoms of tinnitus and deafness are reported to have been present from the onset of streptomycin therapy, which is an unusual time relation for this toxic manifestation. Other toxic effects noted occasionally in the series were rashes, fever, pain at sites of injection, headache and flushing, none of which were alarming although the patient receiving 8 Gm. a day experienced extreme prostration and tachycardia of such severity that treatment was discontinued. No patients in this group showed renal damage which could be attributed to streptomycin.

#### COMMENT

At present, it is impossible to make definite statements as to the precise place of streptomycin in the treatment of bacterial endocarditis. Certainly penicillin is the drug of choice for the majority of cases. In the rare case in which the infecting organism is resistant to penicillin or in those instances in which maximal doses of penicillin have failed, streptomycin offers some hope. The value of *in vitro* tests of streptomycin-sensitivity in predicting the outcome of therapy cannot yet be determined but it is to be noted that, in the present series, treatment was not successful in any case in which the organism required more than 8 micrograms per cc. for *in vitro* inhibition of growth.

TABLE I  
PATIENTS WITH BACTERIAL ENDOCARDITIS TREATED WITH STREPTOMYCIN

Case No.	Infecting Organism		Streptomycin Therapy			Result	Toxicity	Remarks
	Type	Streptomycin Sensitivity $\mu$ /cc.	Daily Dose Streptomycin (Gm.)	Duration of Therapy (Days)	Total Dose (Gm.)			
1.	Unidentified gram-negative bacillus	3.75	3	10	30	Cure	Histamine-like	Also received sulfadiazine
2.	<i>B. pyocyaneus</i>	15	3-6	27	104	Failure	Severe vestibular	
3.	Unidentified gram-negative bacillus	1-2	3	21	63	Cure?	Vestibular	2 months follow-up
4.	<i>Enterococcus</i>	8-40	3	14	42	Failure	.....	Blood level averaged 51
5.	<i>Enterococcus</i>	3.5	4	32	125	Cure	Vestibular	Penicillin also given
6.	<i>Enterococcus</i>	20-<100	6	7	42	Failure	.....	Organism became fast
7.	Unidentified gram-negative bacillus	1-16	2.5	40	100	Failure	Vestibular and auditory, marked	Temporary response, organism became resistant
8.	<i>H. influenzae</i>	1.5-2	2	10	20	Cure	.....	Also penicillin and sulfadiazine
9.	<i>B. aerogenes</i>	.....	2	7	14	Failure		
10.	<i>Ps. aeruginosa</i>	40	2-4	24	88	Failure		
11.	Unidentified gram-negative bacillus	7	2.6-3.2	20	50	Cure?	Vestibular	Penicillin also
12.	<i>Staph. aureus</i>	0.4	1.5-3	28	72	Cure	Vestibular and auditory, improving	Penicillin sensitivity 10 units
13.	<i>Strep. viridans</i>	5	2	14	28	Failure		
14.	<i>Strep. viridans</i>	5	3	34	102	Cure?	Vestibular	3 months follow-up
15.	<i>Strep. viridans</i>	.....	3 for 1 day, then 1	15	17	Cure?	.....	3 months follow-up
16.	<i>Strep. viridans</i>	.....	2	17	33	Failure		
17.	<i>Enterococcus</i>	a) 4	4	5	20	Remission 3 months	.....	Blood levels 25-50
		b) 0.2-15	1-8	28	72.5	Failure	Fever and prostration on 8 Gm.	Blood levels up to 180
18.	<i>Enterococcus</i>	.....	3	32	105	Failure	.....	Temporary clinical improvement

Decisions as to dosage and duration of therapy must still be made largely on the basis of analogy with the use of penicillin in this disease. Treatment should probably be continued for three to four weeks at a daily dosage of from 2 to 6 Gm. Although

this means that one can expect almost uniform appearance of vestibular damage and probably a significant incidence of nerve deafness, there are obvious reasons for accepting these risks. In the first place, patients with an established diagnosis of

bacterial endocarditis which is not amenable to therapy with penicillin have a virtually hopeless prognosis without streptomycin. Secondly, large doses of streptomycin are recommended because of the marked tendency of bacteria to become resistant to this agent when exposed to it in sublethal concentrations. The suggested duration of therapy is based mainly on experience with penicillin treated cases, and is therefore quite tentative. Though one would feel safer in continuing a course of streptomycin for three or four weeks, in individuals who appear to be doing well but who develop evidence of eighth nerve deafness after two weeks, it may be wise to stop at that point, for the acoustic damage has been shown to regress if the drug is promptly withdrawn.

What will be accomplished in difficult cases with combinations of two or more antibiotics administered together remains to be seen, but there are reasons for believing that such an approach might be fruitful. In cases treated with a single drug some therapeutic failures seem to be caused by the persistence of a very small number of the original population of organisms. These may be a few bacterial cells which in the beginning were more resistant to the antibiotic than their fellows, or they may be cells in a temporary phase of resistance. In either event it seems reasonable to suppose that if they were caught in a crossfire of two antibiotics acting at the same time but in different manners, the chances of their survival might be lessened. Furthermore, certain individual cells in a bacterial population might be able to resist the action of penicillin but would succumb to streptomycin, while at the same time other individuals might do the reverse. It is important to note that such events could be taking place and not be apparent in the *in vitro* determinations of sensitivity. As usually performed, these tests tell one only what

happens to the great majority of the cells in a culture, and a few slow-growing individuals could be missed. In this connection, it is of interest to note that in some patients with bacterial endocarditis in early relapse after the penicillin therapy, blood cultures had to be incubated for almost three weeks before growth was detectable.

#### RECOMMENDATIONS

Tentative recommendations as to the use of streptomycin in bacterial endocarditis may be stated as follows:

1. The infecting organism should, whenever possible, be isolated and its sensitivity to streptomycin and penicillin determined.
2. In most cases of non-hemolytic streptococcus endocarditis, penicillin in large dosage is the drug of choice.
3. The following varieties of bacterial endocarditis should be given a trial with streptomycin therapy: (1) Infections due to gram-negative bacilli; (2) infections due to penicillin-resistant gram-positive cocci, and (3) infections which have failed to respond to maximal penicillin therapy.
4. Dosages of from 2 to 6 Gm. daily for two to four weeks should be used, depending on the sensitivity of the organism and the clinical response.
5. It is important that large doses be given from the start of treatment because of the marked tendency of organisms to develop resistance to streptomycin.
6. A high proportion of patients so treated must be expected to show vestibular damage, and a few may show nerve deafness as a result of streptomycin toxicity. Audiometric and vestibular function tests should be done before therapy and at weekly intervals during treatment with streptomycin.
7. In clinically resistant cases of endocarditis caused by organisms which show some *in vitro* sensitivity to both penicillin

and streptomycin, a course of therapy with both drugs together should be tried.

#### SUMMARY

Results of treatment of eighteen cases of bacterial endocarditis with streptomycin are presented and discussed. Eight patients appear at present to be cured. Indications for the use of streptomycin in bacterial

endocarditis are considered and tentative recommendations for treatment made.

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# Streptomycin in Peritonitis\*

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PERITONEAL infections have always been difficult to treat clinically. There can be no doubt but that the sulfonamides and penicillin have been useful in the treatment of peritonitis, but it cannot be said that these agents control all peritoneal infections even when they are used in addition to adequate surgery and adequate supportive therapy. Because of their limited antibacterial activity neither penicillin nor the sulfonamides would be expected to control completely peritoneal infections of mixed gram-positive and gram-negative organisms. Also it is well recognized that some of the body exudates have an inhibitory effect on the sulfonamides and that the action of penicillin is inhibited by certain bacterial products.

Streptomycin, because of its range of antibacterial activity, would appear to be an ideal agent with which to treat mixed peritoneal infections. Streptomycin is not destroyed by body exudates nor by the action of bacteria or bacterial products. Preliminary clinical experience and a more extensive experience in the treatment of experimental peritonitis indicate that streptomycin is useful in the treatment of peritonitis.

Keefer<sup>1</sup> reported on the treatment of fifty-three patients with peritonitis in his report of the first 1,000 patients treated with streptomycin under the direction of the Committee of Chemotherapeutics and Other Agents of the National Research Council. He points out the difficulty of evaluating the precise rôle of any form of chemotherapy in the treatment of peritonitis for the reason

that there are so many variables concerned in recovery from this type of infection. Of the fifty-three patients with peritonitis thirty-nine recovered. Of the twenty-one patients with peritonitis following appendicitis three died. Of nine patients with peritonitis which we have treated with streptomycin or a combination of streptomycin and penicillin only one patient has died. This patient had a carcinoma of the sigmoid colon which ruptured several days before admission to the hospital. Following surgical drainage of the abdomen the patient lived for forty-six days and finally succumbed to multiple abdominal abscesses. One of the abscesses communicated with the colon presumably at the point of the original perforation. Because of the difficulty of evaluation of the many variables in the treatment of peritonitis clinically, an attempt was made to determine the relative usefulness of streptomycin and streptomycin in combination with various other antibacterial agents in the treatment of experimental peritonitis in animals.

Murphy, Ravdin and Zintel<sup>2</sup> demonstrated that streptomycin is effective in the treatment of experimental peritonitis in dogs. Streptomycin therapy in the dosages used resulted in a 40 per cent greater survival rate in the treated group than in the control group. Penicillin therapy according to the data of Fauley et al.<sup>3</sup> produced a 34.2 per cent greater survival rate in the treated animals than in the control animals if the animals which developed fistulas were not excluded. Although the Fauley technic was used by both groups of investigators, their

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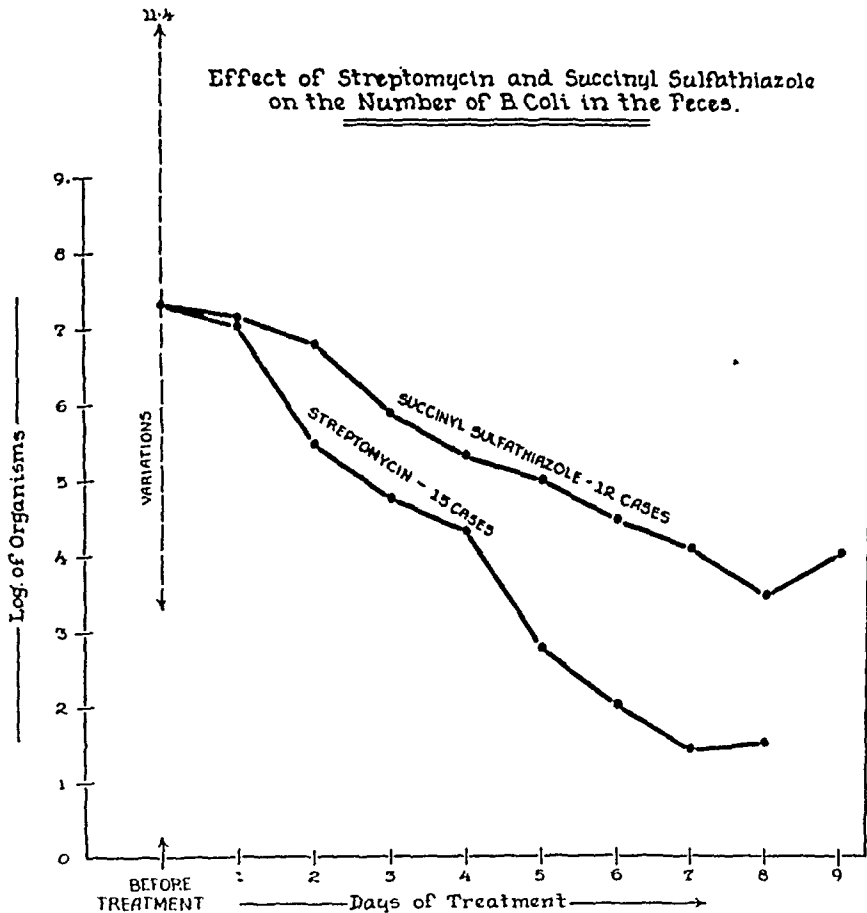


FIG. 1. Effect of streptomycin and succinylsulfathiazole on the number of B. coli in the feces.

results cannot be compared directly because of the discrepancy in the survival rates of the respective control groups, namely, 7.4 per cent reported by Fauley et al. and 30 per cent reported by Murphy et al. Bower et al.<sup>4</sup> found that 50 per cent of the animals treated with sulfanilamide lived whereas 91.7 per cent of his control animals with experimental peritonitis died. Thus in the hands of different investigators sulfonamides, penicillin and streptomycin have each produced survival rates 34 to 41.7 per cent greater than the respective control survival rates.

Further experiments were designed to compare the effectiveness of combinations of the chemotherapeutic and antibiotic agents. Although the use of multiple agents in the treatment of infections has not been recommended in the past, there are some indications that may justify multiple ther-

apy. The use of several agents with different ranges of antibacterial activity might well be considered reasonable in the treatment of peritonitis which is usually an infection of several types of gram-positive and gram-negative organisms. The use of such combinations of agents might further be justified by the fact that often it is not possible to know the complete bacteriological picture of peritoneal infections and, therefore, is impossible to know whether a therapeutic response could be expected from a single chemotherapeutic or a single antibiotic agent. Furthermore, it has been shown by Nichols<sup>5</sup> that penicillin and streptomycin have a synergistic action against certain bacterial organisms and certain combinations of bacterial organisms. In other words, the actions of penicillin and streptomycin under given conditions are more than

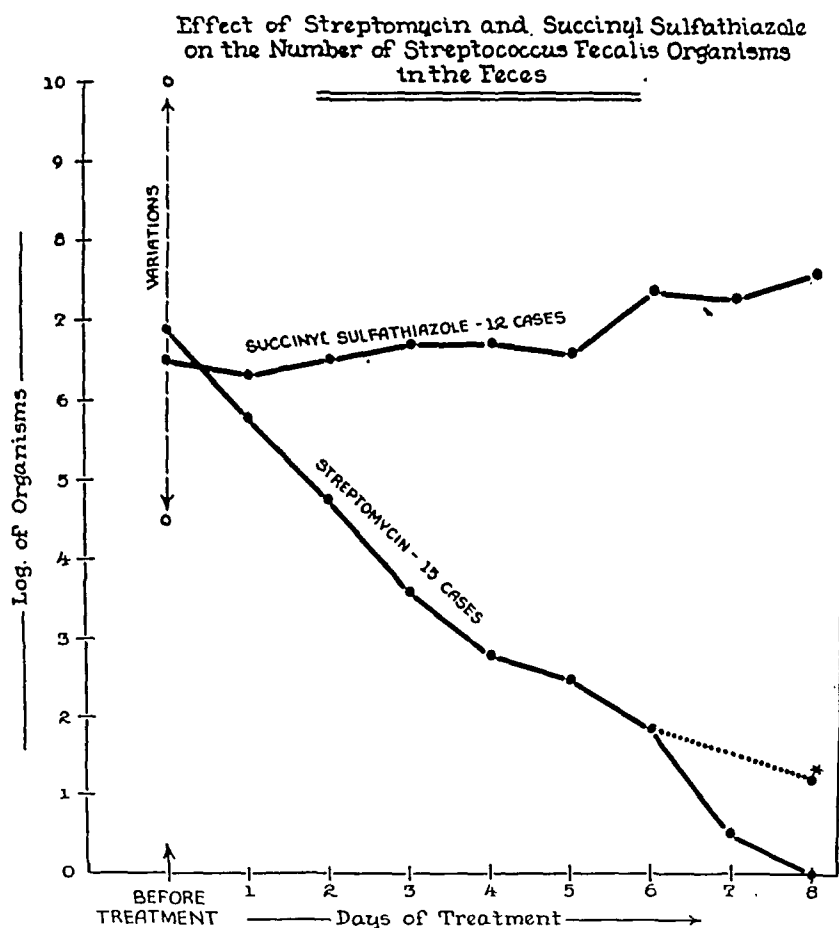


FIG. 2. Effect of streptomycin and succinylsulfathiazole on the number of Streptococcus fecalis organisms in the feces.

additive. Finally Carpenter<sup>6</sup> has shown that the ability of a given organism to develop resistance *in vitro* is almost abolished by subjecting the organism to several antibacterial agents simultaneously.

Five groups of animals were used to compare the effectiveness of streptomycin with various combinations of antibacterial agents in the treatment of peritonitis. A more virulent type of peritonitis was produced in these animals than is produced by either the Bower or the Fauley technic and, therefore, the following figures cannot be compared with those cited in the preceding discussion. In our experiments, after ligating the blood supply to the appendix with silk ligatures, the base of the appendix was ligated with umbilical tape. The appendix was opened along its entire length. With the aid of an

Allis clamp the peritoneal cavity was contaminated with the appendiceal contents. Finally, after closing the abdominal wound, the dogs were given 55.0 cc. of castor oil. The survival rate following streptomycin therapy was 27.4 per cent as compared to the control survival rate of 6.6 per cent. Streptomycin alone was not as effective as was the combination of local sulfanilamide, systemic sodium sulfadiazine and systemic penicillin, as evidenced by a survival rate of 40 per cent following the combined therapy.<sup>7</sup> Sixty per cent of the animals survived when streptomycin therapy was added to the local sulfanilamide, systemic sodium sulfadiazine and systemic penicillin therapy. Thus streptomycin had an added protective effect over and above that afforded by the sulfonamides and penicillin in the dosages used. Finally,

Effect of Streptomycin and Succinyl Sulfathiazole  
on Number of Clostridial Organisms in Feces

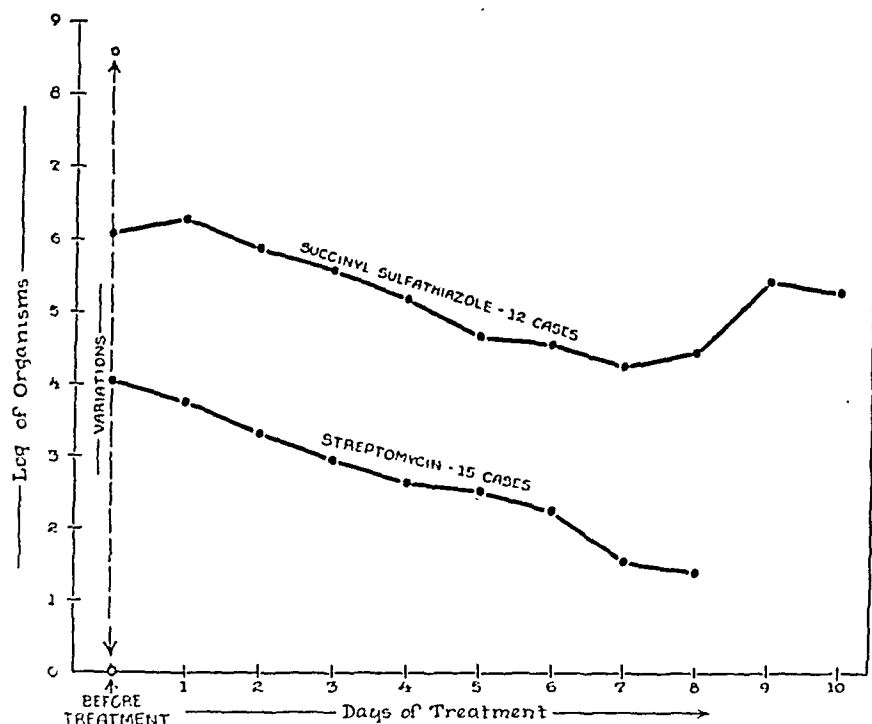


FIG. 3. Effect of streptomycin and succinylsulfathiazole on number of clostridial organisms in the feces.

the survival rate of 70 per cent in the animals treated only with penicillin and streptomycin systemically<sup>8</sup> was greater, but not significantly greater, than the 60 per cent survival rate observed in the animals treated with local sulfanilamide, systemic sodium sulfadiazine, systemic penicillin and systemic streptomycin. On the basis of these experiments the combination of penicillin and streptomycin would appear to be as effective as any of the other combinations of antibacterial agents used.

#### PROPHYLACTIC STREPTOMYCIN PRIOR TO LARGE BOWEL SURGERY

Streptomycin when administered by the oral route appears to be the most effective agent for reducing the relative number of bacterial organisms in the feces. Following oral administration 95 to 98 per cent of the streptomycin is recovered in the feces. Concentrations of from 4,000 to 13,000 micro-

grams of streptomycin per Gm. of feces are usually attained after the administration of 1.0 Gm. of antibiotic daily for several days. Since streptomycin is not destroyed appreciably by the gastric juices, it can be administered, dissolved or suspended, in any liquid such as milk, fruit juice, etc. There seems to be no difference in antibacterial effect whether it is given in four divided doses every six hours or whether it is administered in three divided doses—one with each meal. Oral streptomycin is more potent than succinylsulfathiazole in its effect on the bacterial flora of the stools. Streptomycin is not only more effective in reducing the number of *Bacillus coli* organisms, but it is also more effective in reducing the number of *Streptococci fecalis* and *Clostridial* organisms than is succinylsulfathiazole. Although some organisms completely disappear from the stools, complete sterilization of the large bowel was not attained. Using

Effect of Streptomycin  
in Primary Resection of the Left Colon.

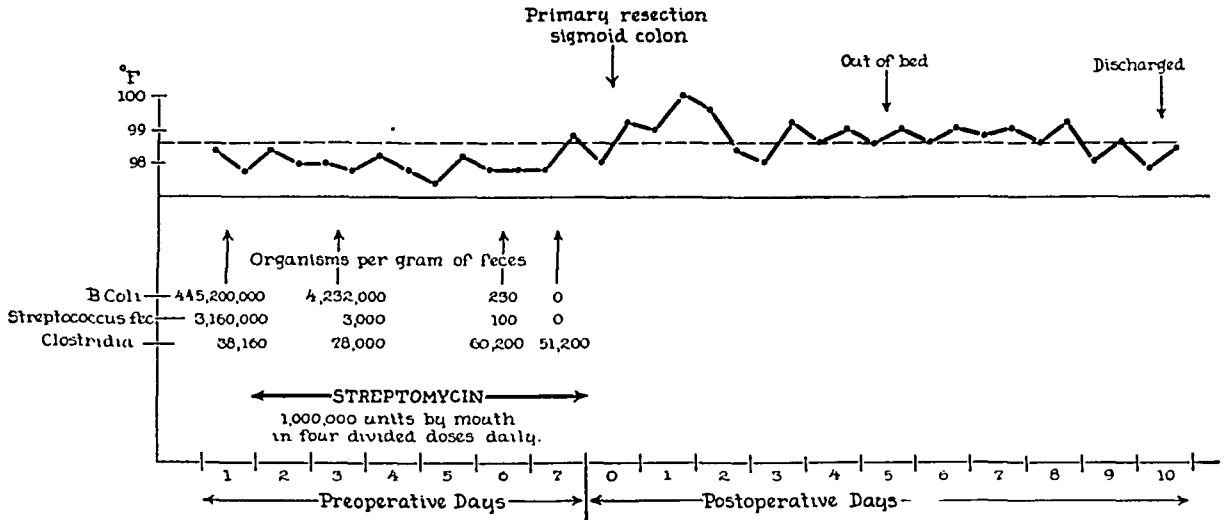


FIG. 4. Preoperative and postoperative effect of streptomycin in a patient who had a primary resection and anastomosis of the sigmoid colon.

massive doses of streptomycin, succinylsulfathiazole and sulfaguanidine, Smith and Robinson<sup>9</sup> were unable to sterilize the feces of rats. There is reasonable doubt that complete sterilization can be attained since occasional strains of bacterial organisms found in the feces are resistant to the action of streptomycin and to sulfasuxidine.

Streptomycin was administered in doses of 1.0 Gm. per day to fifteen patients for periods of from six to ten days. Quantitative stool cultures were carried out by Miss Marjorie Wiley before treatment was started and at two-day intervals thereafter. By plating out stool suspensions on differential media, counts were obtained for the coliform group of organisms, *Streptococcus fecalis* and *Clostridia*. The results were compared with similar data obtained by Lockwood and Zintel<sup>10</sup> previously with succinylsulfathiazole. With both drugs, occasional patients show marked deviations from the mean. The logarithms of the counts were plotted against time of drug administration and an average curve was drawn for each drug and each group of organisms. The relative effectiveness of succinylsulfathiazole

and streptomycin on *Bacillus coli*, *Streptococcus fecalis*, and the clostridial organisms is shown in Figures 1, 2 and 3. The figures used are the average of the logarithms, not the logarithm of the averages. Streptomycin, even in the limited dosage employed, was much more effective than was succinylsulfathiazole.

The argument in favor of the prophylactic use of agents to reduce the number of bacterial organisms in the large bowel contents prior to elective surgery is largely a theoretical one but with apparent practical importance. The mortality rate of peritonitis following elective surgery of the large bowel at the Hospital of the University of Pennsylvania in the last three years prior to the use of streptomycin was but 1 per cent. Several thousand cases would be required to demonstrate a significant difference in mortality rate between patients who received oral streptomycin and those who did not.

It is well known that in animal experiments the possibility of producing an infection depends upon three variables: (1) the virulence of the organisms, (2) the resistance of the host, and (3) the number of bacteria

present. Granted faultless surgical technic and supportive therapy, including chemotherapy and antibiotics, the first two factors would be fixed for any given patient. The last factor, that of the number of organisms present, may be altered by the preoperative use of oral streptomycin. Regardless of whether an open or a so-called "aseptic," or closed, method is used, some bacteria of the bowel content gain access to the peritoneal cavity during any operative procedure on the large bowel. In the very occasional patient, regardless of the operative method, there is gross spillage of fecal material. A very small percentage of patients may have fecal contamination secondary to necrosis of the tissue or leakage of the suture lines after operation. It seems reasonable to assume that the patient who has had the bacterial content of his fecal stream reduced approximately 180,000 times (as in the case of *Bacillus coli*) will have a better chance of escaping peritonitis than the patient who did not have the benefit of preoperative oral streptomycin.

We believe that with the aid of the antibiotic agents we are able to do a greater number of large bowel resections with primary suture. Figure 4 shows the preoperative and postoperative course of a patient who had a resection and primary suture of the bowel for carcinoma of the sigmoid colon, who was prepared with streptomycin

orally and who received streptomycin and penicillin postoperatively. Although the total number of patients treated with streptomycin orally is much too small to attempt to draw any conclusions, we have been impressed with the smoothness of their postoperative courses and the absence of evidences of peritoneal infection.

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# Topical Use of Streptomycin in Wounds\*

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AFTER the demonstration by Florey and Cairns<sup>1</sup> that the topical application of penicillin would not hasten the resolution of established infection in wounds, the reason for this failure was sought. Penicillinase,<sup>2</sup> a powerful substance that destroyed penicillin, was known to be elaborated by and was finally isolated from the gram-negative bacilli.<sup>3</sup> The gram-negative bacilli *E. coli*, *pyocyaneus*, *proteus*, etc., which invariably come to inhabit the pus of infected wounds as contaminants of fecal origin and with enormous capacity to spread, are not destroyed by penicillin. Their persistence, therefore, seemed to explain why the gram-positive bacteria continued to proliferate in spite of the addition of penicillin to the wound.

This failure of penicillin to cure by topical application the established localized infection in the wound must not be confused with its excellent efficacy to combat wound cellulitis and septicemia when administered parenterally.

With this background, the best approach to rid the wound of penicillinase seemed to be to destroy the gram-negative bacilli by using another antibacterial substance in conjunction with penicillin. Until this conclusion was reached, however, the need for an antibacterial to destroy only gram-negative bacilli had not received much attention although urologists had recognized the significance of this group of bacteria and had found them difficult to destroy in infections of the urological tract. In the "antiseptic era" antibacterial substances theoretically destroyed the gram-negative

bacilli as well as others (and also the tissues) and later the failure of the sulfonamides, except for sulfamylon, to act in the presence of pus was attributed to para-aminobenzoic acid and not to any substance elaborated by the gram-negative bacilli.<sup>4</sup> True, the sulfonamides did not destroy the gram-negative bacilli in mixed infections but an adjunct antibacterial substance was not sought because of the apparent uselessness of the sulfonamides in the presence of pus.

Moreover, whether the gram-negative bacteria are really virulent or are simply contaminants of pus had often been discussed. They appear late in the pus and in spite of the fact that they finally dominate the flora. The granulations may grow abundantly and contraction takes place without interference.<sup>5</sup> Perineal wounds were pointed to as evidence that these micro-organisms did not interfere with healing. Gram-negative bacilli were always present in these wounds and yet they healed with bright red granulations. Some even believed that an enzyme secreted by the gram-negative bacilli, or in the inflammatory reaction to them, liquefied slough and that as soon as slough was liquefied the discharge of pus ceased. However, only one or two of the least common variety actually secrete a collagenase<sup>6</sup> so that the non-specific inflammatory reaction must be responsible for this enzymatic action.

The opponents to the thesis of the benignity of gram-negative bacilli pointed out that the profuse discharge produced in response to them depleted the serum protein of the patient, prevented the spread of skin

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grafts, and even liquefied grafts successfully transplanted.<sup>7</sup> They emphasized also that gram-negative infections do not clear up in tissues like bone which do not liquefy. Lastly, it cannot be denied that the exudative phase of healing of the perineal wound would be shorter if a non-toxic gram-negative antibacterial substance were used to prevent the initial multiplication of these bacteria.

In summary then, gram-negative bacilli do create infections in wounds and in the urinary tract, although this fact did not receive adequate attention until after an antibacterial substance was available to destroy gram-positive bacteria without interfering with the healing of the wound.

Before the isolation of streptomycin by Waksman,<sup>8</sup> no satisfactory antibacterial substance was found to destroy the gram-negative bacilli. Agents like acetic acid that were thought to be specific only decolored them. Most of the antibacterial substances tested for this purpose were either too toxic to cells and prevented wound healing or they destroyed penicillin. Penicillin is, of course, extremely sensitive to changes in environment. Suitable agents exhibiting low cell toxicity were difficult to find because the metabolism of the gram-negative bacilli more closely resembles the metabolism of the tissue cells than does that of the gram-positive bacteria.<sup>9</sup> All the common anti-septics except parachlorophenol failed on both scores and this substance was found to be mildly toxic to fresh tissues but not to granulations. Streptothrycin, first isolated by Waksman,<sup>10</sup> was somewhat compatible with penicillin but it was definitely toxic to cells and interfered with wound healing.<sup>11</sup>

Streptomycin, on the other hand, was not toxic to fresh cells in concentrations of 200 units per cc. and did not interfere with healing of the rabbit's ear wound.<sup>11</sup> Granulations are not affected by 1,000 units of streptomycin per cc. At a concentration of 200

units per cc., streptomycin was bactericidal after a short period of contact with the bacteria, acted in the presence of pus and to date there is no evidence that topical application produces untoward side effects. No cases of flushing, skin rashes or tinnitus have been encountered following local use of streptomycin. Neither Brown and Hinshaw<sup>12</sup> nor Fowler and Ewing<sup>13</sup> have reported otic complications from the local application of streptomycin. In all fairness, however, it must be noted that streptomycin has not been used in such large quantities topically, and that most patients have received the drug parenterally.

TABLE I  
STREPTOMYCIN 200 UNITS PER CC. 10 MINUTE CONTACT

Strain of Bacteria	Inhibition of growth of bacteria in area contacted by paper	Inhibition zone about this area
B. coli .....	++++	++
B. coli .....	++++	++
B. coli .....	++++	+
B. proteus .....	++++	+
B. proteus .....	++++	+
B. proteus .....	++++	++++
Staph. (coagulase positive) .....	++++	++
Staph. (coagulase positive) .....	++++	++++
Pyocyanus .....	+++ Spread in from edges	0
Pyocyanus .....	+++ Spread in from edges	0
Pyocyanus .....	++ Overgrown in 36 hours	0
Streptococcus hemolytic .....	0	0
Green streptococcus ..	0	0

The bacterial spectrum of streptomycin includes micro-organisms other than the gram-negative bacilli. In fact, it is more inclusive than penicillin but unfortunately streptomycin does not have a complete bacterial spectrum. In our own testing, both the hemolytic and green streptococci were not destroyed by the concentrations used. (Table I). Pulaski<sup>14</sup> found that 80 per cent of

TABLE II

STREPTOMYCIN SENSITIVITY OF AEROBIC BACTERIAL FLORA OF 143 SURGICAL INFECTIONS

Streptomycin units/cc. ( <i>in vitro</i> )	0.5	1	2	4	8	16	32	64	128 +	Total
Gram-negative organisms										
A. aerogenes.....		3	8	10	4	4	2	3	3	37
Esch. coli.....		1	5	10	12	5	2			35
Paracolon group.....			5	3	7	3		1	1	20
K. pneumoniae, type A.....		1	4	7	4	1	1	1	1	20
K. pneumoniae, type B.....			9	5	4	1	1		3	23
K. pneumoniae, no type.....				1						1
P. vulgaris.....	1		5	9	38	22	5	4	1	85
P. morganii var.....			1	3	8	3	2	1	3	21
Ps. aeruginosa.....				1	12	23	8	1	8	53
Totals.....	1	5	37	49	89	62	21	11	20	295
Gram-positive organisms										
Micrococcus.....	1	1								2
Staph. albus.....	2			1						3
Staph. aureus, hemolytic.....	20	19	7	15	7	2	1	1	19	91
Staph. aureus, non-hemolytic.....	3	2	1						2	8
Hemolytic strep. beta, aerobic.....	1			3	5	3			2	14
Hemolytic strep. beta, microaero.....	1	1	1							3
Str. viridans, aerobic.....		4	2	3	8	6	3	1	6	33
Str. viridans, microaero.....									2	2
Non-hemolytic strep., aerobic.....	7		2	12	9	19	4			53
Non-hemolytic strep., microaero.....							1			1
Diphtheroids.....	15	4	5				1	1	15	41
B. subtilis.....			1		2					3
Totals.....	50	31	19	34	31	30	10	3	46	254
Grand totals.....	51	36	56	83	120	92	31	14	66	549

Pulaski, Edward J.: Bulletin of U. S. Army Medical Department, November, 1946.

the bacteria tested (Table II) were destroyed by 32 units per cc. of streptomycin but even at higher concentrations some strains were not affected. Hirshfeld<sup>15</sup> found that with 256 units of streptomycin some strains were unaffected.

Thus, if penicillin were used alone the gram-negative bacteria would not be destroyed in the wound and they in turn would destroy penicillin; while if streptomycin were used alone all bacteria would not be destroyed and, moreover, some of the sensitive ones quickly become resistant.<sup>14</sup> For this reason, and because the flora of traumatic and clean-contaminated wounds always evolves through a mixture of gram-positive and gram-negative bacteria, even though one species may come to dominate the flora at one time, combinations of these anti-

biotics should always be used for topical applications.

Penicillin would have to be added fresh to the correct concentrations of streptomycin, however, because most varieties of penicillin rapidly lose potency on standing in solution. The solution of streptomycin is slightly acid, pH 5.6–6.5, and this acidity slowly destroys penicillin. The length of time that penicillin will maintain its strength in buffered streptomycin has not been determined. Because of these difficulties, it has been suggested that 5 per cent sulfamylon be used in place of penicillin. Ampules of this mixture will keep and can be sterilized. Sulfamylon is about as effective as penicillin;\* it is non-toxic at this con-

\* Penicillin is more powerful when the strains are susceptible.



centration, compatible with streptomycin, bactericidal and it acts quickly in the presence of pus. This concentration of sulfamylon and streptomycin encounters few resistant strains of bacteria. (Table III.)

TABLE III  
STREPTOMYCIN 200 UNITS PER CC AND MARFANIL 5% AND  
0.5% SODIUM BENZOATE

Strain of Bacteria	Inhibition of growth of bacteria in area contacted by paper	Inhibition zone about this area
Staph.....	++++	++
Staph.....	++++	++++
Staph.....		
Staph.....	++++	+++
Staph.....	++++	+++
Staph. and B. coli.....	++++	+++
B. coli.....	++++	+++
B. coli.....	++++	+++
Proteus.....	++++	+
Proteus.....	++++	++
Pyocyanus.....	++++	++
Pyocyanus.....	++++	++
Hemolytic strep.....	++++	+++
Green strep.....	++++	+

Topical application of this mixture of antibacterials immediately places in the wound a higher concentration of these substances than could be obtained by parenteral therapy. As a result, a higher concentration is obtained sooner, by osmosis, inside tissues separated from blood supply. Parenteral therapy, for example, at best yields a blood concentration of 36 units of streptomycin and 30 units of penicillin while topical application can puddle in 200 units of penicillin or 200 units of streptomycin and 5 per cent sulfamylon, all within limits that do not interfere with the vitality of cells.

Tissues separated from blood supply in the wound always determine the issue as to infection. In the fresh wound, the tissue separated from blood supply is one of a triad with bacteria and foreign bodies that initiates infection. Although débridement

removes dead tissue and foreign bodies and is successful thereby in preventing infection, complete débridement cannot always be accomplished nor can it always be done in time. Therefore, topically applied antibacterial substances provide the extra safety factor to prevent infection. In older wounds the tissues separated from blood supply that have not sloughed determine the chronicity of the infection.

The concentration of antibacterials in the tissues surrounding the wound differs according to circumstances. In the fresh wound, the vascular system in the surrounding tissues always leaches away and dilutes the antibacterial applied locally after a certain depth of penetration into the tissues. This leaching is greatest and occurs on the surface when there are young granulations present in the surrounding tissue. Leaching is least when there is local edema in the surrounding tissues, as occurs shortly after wounding. In general, an effective bactericidal level in the surrounding tissues is best maintained through parenteral therapy but a concentration can be obtained immediately and for a short period of time after wounding by injecting streptomycin and penicillin or sulfamylon of the correct concentration without causing harm locally. This superconcentration helps prevent infection and initiates parenteral therapy.

The following laboratory experiments will illustrate the effectiveness of this form of therapy. Crushed wounds were produced in the back of rabbits and contaminated with particular bacteria or with floor contamination. All developed infections in their wounds and up to 25 per cent of these animals died of septicemia. This mortality was reduced to zero by parenteral administration of penicillin and streptomycin and it was also reduced to zero by injecting 20 cc. of the mixture of streptomycin and sulfamylon in the tissues about the wounds after they were washed with the same solution.

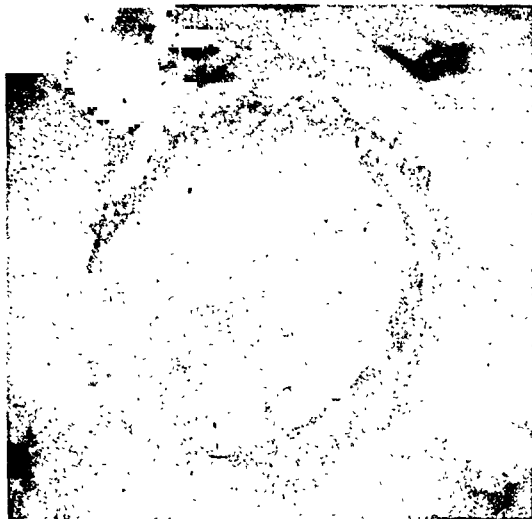


FIG. 1. Infected wound; tissue crushed and contaminated five days before. Center is necrotic; profuse discharge of pus; direct smear made on blood plate shows many bacteria; wound definitely infected.

In these wounds the therapy was more effective in preventing infection than in shortening the resolution of established infection.<sup>16</sup> Moreover, infection was more easily prevented in fresh wounds than in those treated several hours after injury. Thus, infection was prevented in wounds treated immediately by washing and injecting the surrounding tissues with 20 cc. of streptomycin, 200 units per cc., and sulfamylon 5 per cent. (Figs. 1 and 2.) No attempt was made to débride the crushed tissue.

On the contrary, when the period between infliction of the wound and the time of therapy became greater than three hours, then the use of the mixture of antibacterials did not prevent infection unless the wound was freshened by débridement. With débridement and local chemotherapy, infection was prevented experimentally as late as forty-eight hours after wounding. The time limits when this combined therapy will no longer be effective have not been determined. Neither has the effectiveness of the mixture of sulfamylon and streptomycin been investigated as to its capacity to decon-



FIG. 2. Tissue crushed and contaminated five days before; however, this has been treated immediately by washing with mixture of streptomycin and sulfamylon. Surrounding tissues also injected with 20 cc. of mixture; no débridement of crushed tissue was carried out; the base of wound is filled with bright red granulations; there was no discharge of pus. Direct smear showed only occasional bacteria. The wound continued to heal without evidence of infection.

taminate wounds before delayed primary suture is carried out.

Despite the success of the immediate use of this mixture of streptomycin to prevent infection experimentally in crushed wounds, no attempt should be made to treat traumatic wounds with it unless the wound is first carefully débrided. These experimental wounds, unlike traumatic wounds, did not contain foreign bodies. On the other hand, as has already been mentioned, because all injured tissue cannot always be débrided from traumatic wounds and because the procedure cannot always be carried out early, employment of the combination of streptomycin and sulfamylon or penicillin locally at the time of the débridement will definitely help to prevent infection.

Clinically heavily contaminated operative wounds have been washed immediately with this combination of antibacterials and infection prevented. These wounds, that are made clean and then contaminated,

contain a minimal amount of crushed tissue and foreign bodies, and in them the immediate use of the antibacterial combination corresponds to its use in experimental wounds. In other words, this mixture is a subcutaneous antiseptic—a therapeutic ideal that has been sort for a long time. Its topical use can be highly recommended in surgery of the large bowel and of hemorrhoids.

Why the mixture of streptomycin and sulfamylon failed to work in crushed contaminated wounds three hours after infliction is interesting because the failure of antibacterials and antibiotics to hasten the resolution of the established infection has, in part at least, the same etiology. After three hours the bacteria were found to be just as susceptible to the action of the antibacterials; actually they were fewer in number and contact with them should have been as effective because the solution was injected in both instances. Fibrin was deposited in the injured tissues, of course, and microscopic examination disclosed that many of the bacteria had entered leukocytes. The latter seems to be the most important change because the bacteria were now in a position where the solution could not reach them unless the leukocytes were destroyed or until the bacteria were again freed from the leukocytes. Bacteria freed from leukocytes and not destroyed would be capable of re-initiating infection.

To hasten resolution of the localized established infection, an adjunct chemical substance is definitely needed to implement the action of antibacterial substances. This type of infection invariably subsides promptly when all devitalized tissues disappear from the wounded area and it persists as long as these sloughs are present. Fascias and bone are not readily liquefied by tissue enzymes and their persistence accounts for the chronicity of infection in wounds containing sloughing fascia and in osteomyelitis. To aid in the liquefaction of fascia and

to explode leukocytes containing bacteria, as well as to limit mold growth that inhibits enzymatic digestion, a mixture of acid, glycerine and thymol has been used to clear the wound of puddles of pus and small pieces of slough that cannot be removed with scissors. The acid-glycerine-thymol combination is puddled into the wound and kept there for approximately three hours. This exposure also causes a very slight erythema, the granulations become bright red and they sometimes bleed slightly. The acid is then washed from the wound because it tends to destroy streptomycin and fine mesh gauze saturated with the combination of streptomycin and sulfamylon or penicillin is packed into it. The procedure is carried out daily until the infection disappears. In chronically established local infections where bone is not involved, rapid resolution has been obtained. The amount of drainage decreases within forty-eight to sixty-four hours and granulations soon begin to fill the wound. On the other hand, when osteomyelitis is present, particularly if pyocyaneus is in the flora, only temporary improvement is obtained and then the infection continues although the discharge of pus is less and is better managed. Pulaski<sup>14</sup> has likewise reported the failure of streptomycin to resolve infection in wounds complicated by osteitis.

Persistent gram-negative infections in wounds that are not maintained by the presence of sloughing tissues have been eliminated by the local use of streptomycin. White,<sup>7</sup> for example, has reported that amputation stumps that would not take skin grafts because of the presence of gram-negative bacteria were, in many instances, cleared of infection and thereafter the grafts took successfully.

Streptomycin has been used topically in the rectum for inflammatory disease, particularly for ulcerative colitis. The number

of cases is still too few to judge the efficacy of this form of treatment. Faget\* has reported that streptomycin applied as wet dressings and in an ointment has healed indolent ulcers on the legs of lepers. The nature of the proper ointment base to use with streptomycin for topical therapy has not been worked out. Such an ointment should be useful in treating diseases of the perineal region.

#### SUMMARY

1. For topical application to wounds, a solution of streptomycin of the proper concentration should be used, not the powder. Freshly wounded tissues are not damaged further and wounds heal without interference when the concentration of streptomycin is at 200 units or micrograms per cc. Granulations are not damaged by 1,000 units per cc. At these concentrations, streptomycin is the best non-toxic antibiotic that has been found to date for gram-negative bacilli.

2. Penicillin, up to 1,000 units, or sulfamylon 5 per cent should always be combined with streptomycin when it is used topically because streptomycin does not have a complete bacterial spectrum at its proper concentration and some susceptible bacteria rapidly acquire resistance to streptomycin alone.

3. Conversely, streptomycin should always be used topically with penicillin because streptomycin kills gram-negative bacilli that penicillin is unable to destroy and these elaborate penicillinase that in turn destroys penicillin.

4. Gram-negative bacilli are almost always present at some time in the evolution of the bacterial flora of wounds even though only a single strain of bacteria may be isolated at one time. Gram-negative bacilli usually dominate the flora of chronically

infected wounds, accounting in part for the failure of topical application of penicillin alone in this type of wound.

5. Gram-negative bacilli definitely interfere with the healing of wounds despite arguments that have been advanced that they are mere contaminants of pus.

6. Because of its stability, sulfamylon 5 per cent makes a better combination with streptomycin than with penicillin. Sulfamylon has a wider bacterial spectrum than penicillin though it is not always as powerful and it acts rapidly in the presence of pus. It can be used with any form of parenteral therapy. This mixture encounters few resistant strains of bacteria.

7. Topically, the solution of streptomycin and penicillin or sulfamylon will prevent infection in wounds better than it will hasten the resolution of established infection, except in certain instances in which no slough is present.

8. In the presence of crushed tissue, prevention of infection can be obtained experimentally until three hours after wounding by washing the wound and injecting about 20 cc. of the solution in the surrounding tissues. With débridement of crushed tissue, prevention of infection has been effected as late as forty-eight hours after wounding when the solution is employed in the same manner.

9. All devitalized tissue cannot be débrided from traumatic wounds nor can the process always be done in time; therefore, topical application of the solution of streptomycin and penicillin or sulfamylon is recommended in the treatment of traumatic wounds as a safety factor to prevent infection.

10. The solution of streptomycin and penicillin or sulfamylon will decontaminate the clean-contaminated operative wound. The solution is applied topically before the wound is closed as one would an antiseptic to the skin.

\* FAGET, G. H. Research in Antibiotics Symposium. Washington, D. C. January 31–February 1, 1947.

11. To hasten resolution of the established localized infection in the wound, adjunct chemotherapy in addition to antibacterial chemotherapy is required. This adjunct chemotherapy must liquefy slough and cause the antibacterial substances to penetrate and kill bacteria in slough and leukocytes.

12. A mixture of acid, glycerine and thymol has been used for this adjunct chemotherapy. It is successful when sloughing fascia is present but it is not successful in the presence of osteomyelitis.

13. Streptomycin alone can rid wounds of persistent gram-negative bacilli infection when no slough is present in the wound. For example, granulations that will not take skin grafts because they harbor a flora of the gram-negative bacilli can be freed of these bacteria by the local application of streptomycin and then skin grafts will take.

14. No otic complications have been observed with the low concentration of streptomycin used topically. However, topical therapy has not been used as frequently nor over such long periods of time as parenteral therapy.

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# The Present Status of Treatment for Influenzal Meningitis\*

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THERE are now available three effective antibacterial agents for treatment of type b H. influenzae infections: sulfadiazine, type b H. influenzae rabbit antiserum and streptomycin. It is already evident that each one when used separately is limited in its curative effect in severe infections. On the other hand under certain circumstances each one can bring about recovery. Evaluation of the separate action of each has become increasingly difficult the greater the number of agents available. This paper will present the results of our attempt over the past ten years to assess the efficiency of each of these therapeutic agents and the indications for their use.

## COMBINED ACTION OF SULFADIAZINE AND TYPE b H. INFLUENZAE RABBIT ANTISERUM

At the beginning the high mortality in influenzal meningitis, over 90 per cent, justified the use of all potentially effective agents. The combined action of sulfonamides and rabbit antiserum specific for type b H. influenzae\* has been used at Babies Hospital for the treatment of meningitis since 1938. This therapeutic program has been simplified and made more efficient by the application of certain principles. The dose of antibody needed varies with the severity of infection. Therefore, some objective criterion of severity is essential. More-

\* H. influenzae type b rabbit antiserum used in this study was supplied by E. R. Squibb and Sons.

\* From the Babies Hospital and the Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York. The work reported in this communication was supported by grants from the Commonwealth Fund.

over the sufficiency of the original dose decided upon requires confirmation.

1. The best index of severity of infection proved to be concentration of sugar in the spinal fluid withdrawn before treatment; the lower the concentration, the greater the severity.

2. Heidelberger<sup>1</sup> showed that the antibody in the rabbit antiserum could be measured by the quantitative chemical method for determining agglutinin and precipitin nitrogen. Mouse protection tests showed that the protective element in the antiserum was actually the anticarbohydrate antibody which this method measured in mg. of antibody nitrogen per cc. Thus it was possible to formulate a quantitative approach to treatment as shown in Table I.

TABLE I SCHEDULE OF DOSAGE ON SPINAL FLUID SUGAR	
Spinal Fluid Sugar (Mg. per cent)	Mg. Antibody Nitrogen Indicated
15	100
15 to 25	75
25 to 40	50
over 40	25

3. This plan aimed to introduce at one time the amount of antibody necessary for recovery. Nevertheless, it was necessary to check its sufficiency. The capsular swelling capacity of the patient's serum following treatment proved to be a good guide. This test was performed daily through the period of activity of infection; and unless it could be shown that the patient's serum contained an excess of free antibody sufficient to cause

capsular swelling of the organisms when diluted 1:10, another dose of antiserum was administered (25 to 50 mg.).

The therapeutic program just described was greatly simplified when it was learned that prompt recovery followed introduction of this antiserum by the intravenous route only. In a given case sodium sulfadiazine is introduced by the subcutaneous route in a quantity equivalent to 0.1 Gm. per Kg. as soon as diagnosis of type b H. influenzae is made. A continuous intravenous drip is set up immediately if there is urgent need of fluids and 5 per cent glucose in saline (approximately 30 cc. per Kg.) is administered over the next hour. Then the quantity of antibody, calculated according to Table 1, is diluted in 10 cc. per Kg. of physiologic saline and added to the reservoir of continuous drip apparatus. The speed is so regulated that the diluted antibody will be administered in two hours. The antiserum may be given by the intramuscular route when necessary; however, in our limited experience a larger total quantity is needed when this route is used. Sulfadiazine is given orally as soon as feasible and continued for seven days after the first sterile spinal fluid is obtained. No additional serum is given unless the capsular swelling test shows inadequate excess of antibody in the patient's serum.

When patients are treated early with the combined therapy of sulfadiazine and type-specific rabbit antibody according to the principles outlined,<sup>2</sup> the response has been so consistent that it is possible to predict not only the outcome but the course of recovery. Even in the fulminating group in which the meningitis progresses so rapidly that the spinal fluid sugar falls to less than 15 mg. per cent within twenty-four hours of onset, prompt recovery can be expected in all cases if sufficient antibody is administered in the initial dose. Actually only 80 per cent of the ninety patients treated ac-

cording to this regimen recovered, the failures being attributable to delay in diagnosis and to unwarranted confidence in the value of sulfonamides alone.

#### SULFONAMIDES

The limitations of sulfonamides as therapeutic agents in influenzal meningitis are now well established. Nevertheless, it is clear that a certain proportion of patients do recover on sulfonamides alone. Our own clinical experience suggests that this fraction is small and we are inclined to believe that the published records of isolated examples of cure with sulfonamides alone convey a false optimism as to the true efficacy of these agents. Over one-fourth of our patients received serum only after extended periods of unsuccessful sulfonamide therapy in other hospitals. Only two-thirds of this group recovered when serum was added; in virtually all of these the infection had been kept under control during treatment but had not been eliminated, for on withdrawal of the drugs recrudescence occurred. This experience led us to study the criteria for selecting those patients who might be expected to recover on sulfonamides alone, and for this purpose we made a comparison of the protective value in mice of available sulfonamides alone, antiserum alone and the best sulfonamide and serum in conjunction. The results established the fact that the efficiency of sulfadiazine, the most effective of three sulfonamides tried, was dependent upon the size of the bacterial population whether in the test tube or mouse and suggested that it might be able to cure meningitis if used early in mild infections. Whereas the protection with sulfonamide alone never exceeded 10,000 M.L.D., when serum was added the mice withstood 1,000,000 M.L.D.<sup>3</sup>

These observations resulted in the adoption of certain criteria for selection of patients who might be expected to recover on sulfadiazine alone. When meningitis has

been present for only twenty-four hours, the infection is judged mild, as indicated by a concentration of sugar in the spinal fluid of 40 mg. or more per 100 cc., and when the clinical features are in keeping with this, the use of sulfadiazine alone is justified initially. If *in vitro* tests indicate usual sensitivity of strain, it is believed that the drug alone may be continued without risk, provided clinical improvement ensues and provided the spinal fluid shows the infection to be under control, with cultures sterile forty-eight hours after the start of chemotherapy. A minimum of two weeks of such treatment is essential for elimination of infection. It is of interest that during a period when approximately thirty patients were treated only two fulfilled the criteria which justified the use of sulfonamides alone. Reports of visiting physicians from Europe indicate that the present mortality rate there in influenzal meningitis is 75 per cent; sulfonamides are the only available therapeutic agents.

TABLE II  
SUMMARY OF PROTECTIVE POWER OF THERAPEUTIC AGENTS  
IN MICE

Therapeutic Agent	Protection	
	M.L.D.	No. of Mice
Sulfanilamide.....	500	120
Sulfadiazine.....	9,250	280
Type b rabbit antiserum.....	28,875	625
Sulfadiazine + serum.....	1,000,000	270
Streptomycin.....	100,000,000	200

It must be emphasized that these therapeutic recommendations refer only to meningitis. Experience with the other varieties of severe infections caused by *H. influenzae*, pneumonia, obstructive infections of the respiratory tract, arthritis, etc., is much less extensive but certain facts are clear. Sulfadiazine alone constitutes an effective

treatment for *H. influenzae* pneumonia in older children. The characteristic clinical syndrome of *H. influenzae* epiglottitis, causing respiratory obstruction, responds promptly to sulfadiazine alone in the majority of patients after tracheotomy.<sup>4</sup> When *H. influenzae* produces pyarthrosis and osteomyelitis, the possibility of injury to epiphysis and cartilage is so great that treatment should aim for the most rapid termination of infection. This is best accomplished by the simultaneous use of all effective therapeutic agents.

#### STREPTOMYCIN

The demonstration by Waksman<sup>5</sup> and other investigators<sup>6</sup> of the antibacterial action of streptomycin on other gram-negative bacilli naturally led to its trial against *H. influenzae*. Investigations were carried out first in the laboratory.<sup>7,8</sup> *In vitro* sensitivity of a number of strains was studied by determining the lowest concentrations of streptomycin which when incorporated in Levinthal agar could completely prevent growth of inocula averaging 700 million organisms after an incubation period of forty-eight hours. All strains tested before exposure to streptomycin were completely prevented from growing by 7.5 units per cc. save for one or two colonies which grew in some tests on an occasional strain on 10 and 13 units per cc.<sup>8,9</sup> *In vivo* the sensitivity was also very great. A single dose of 20 to 80 units per mouse protected mice regularly against more than 1,000,000 M.L.D. (minimal lethal doses); larger doses were effective against 100,000,000 M.L.D. Table II lists for comparison the protective values of the various available therapeutic agents. It is seen that streptomycin's protective power exceeds that of any other single agent and even the combined action of specific rabbit antibody and sulfadiazine. It has been demonstrated that streptomycin actually exerts a rapid lethal action on *H. influenzae*.<sup>10</sup>



After demonstrating the rapid lethal injury resulting from the action of streptomycin on type b H. influenzae, *in vitro* and in the mouse, we were naturally led to explore its therapeutic value in influenzal meningitis. Investigation of the separate action of streptomycin in these patients was difficult for two reasons; first, because most of the patients had already received sulfonamides for a period long enough to reduce the bacterial population, and also because there was already available a treatment which had been shown to be capable of curing virtually 100 per cent of the patients when applied according to certain principles in the first few days of the disease. I refer to the combined action of type specific rabbit antiserum and sulfadiazine. Nevertheless, this trial was considered necessary because if found equally effective, streptomycin could be expected to possess certain advantages over the earlier therapeutic program. Serum sickness could be eliminated. Streptomycin has been shown to be active against all six types of encapsulated H. influenzae as well as the non-encapsulated, non-typable variety of this organism which occasionally causes subacute bacterial endocarditis in adults and meningitis in very young infants. This is true of sulfadiazine also but type b H. influenzae antiserum, the only therapeutic serum available at present, is effective only against type b. However, over 95 per cent of all serious infections caused by the group are due to type b.

**Schedule and Dosage.** Using the dose previously found safe in adults and in a few children treated at Babies Hospital, 20,000 units per pound or 44,000 units per Kg. each twenty-four hours, blood concentrations were determined during two methods of intramuscular administration, by continuous drip and by injections at intervals of three hours. The range of concentrations found is listed in Table III; it is seen that they are sufficient for prevention of growth

of inocula averaging 700 million organisms if the results obtained *in vitro* can be applied to the influence of streptomycin on bacteria in the patient. With the exception of the cases reported<sup>11</sup> all patients have been treated by interrupted intramuscular injections at three-hour intervals. The experience

TABLE III  
VARIATION IN CONCENTRATION OF STREPTOMYCIN BLOOD AND SPINAL FLUID COMPARED WITH MINIMAL EFFECTIVE CONCENTRATION

Case	Concentrations of Streptomycin Units per cc.		Dose and Route of Streptomycin Units in 1,000's			M.E.C. <sup>1</sup> Units per cc.
	Blood *	Spinal Fluid †	I.M.	Each 24 Hours	I.T.	
1	8.9-30.6	9.1-20.4	C.D.	20,000‡	50	2.7
2	5.1-10.1	.....	q3h	20,000	25	2.6
3	4.2- 8.5	5.1-11.5	q3h	20,000	25	4.9
4	10.1-19.1	11.8-20.0	q3h	20,000	25	1.6
5	6.2-14.6	6.2- 6.0	q3h	20,000	50	2.8
6	5.5-14.5	5.0-28.0	q3h	20,000	25	2.8
7	3.3- 6.5	8.5-	q3h	20,000	25	4.4
8	7.3-22.0	4.9-16.3	q3h	20,000	30	7.5
10	5.8-12.2	5.1-12.1	C.D.	20,000	50	2.5
11	9.3-10.5	9.3- 9.6	q3h	20,000	25	1.6
12	7.5- 9.8	11.1-	q3h	20,000	25	4.4

\* Specimen collected at random when intramuscular dose was given by continuous intramuscular drip. When streptomycin was given every three hours the blood was withdrawn three hours after the last dose.

† Spinal fluid concentrations represent those found twenty-four hours after intrathecal dose listed.

I.M., intramuscular; I.T., intrathecal; M.E.C. minimal effective concentration; C.D., continuous intramuscular drip; q3h, every three hours.

‡ Units per pound (0.5 Kg.).

<sup>1</sup> M.E.C., minimal effective concentration of streptomycin necessary to completely prevent growth on Levinthal agar in forty-eight hours when inoculum represents loop from growth on Levinthal agar after six hours' incubation.

of other investigators and our own agree that in meningitis streptomycin must be administered intrathecally; the concentrations present in the spinal fluid after intramuscular use are not adequate. A dose varying from 25,000 to 50,000 units has been introduced daily into the lumbar subarachnoid space. More recently, the first two

intrathecal doses have been given at twelve-hour intervals and 25,000 units have been used as the intrathecal dose in children under three years. There is ample evidence that four to five days of this treatment is sufficient. What streptomycin has failed to accomplish by this time will not be likely to occur after longer periods. If the culture continues to grow, the addition of other therapeutic agents is indicated. The occurrence of eighth nerve deafness and labyrinth dysfunction in a significant number of patients treated for periods longer than one week makes it a serious responsibility to reduce treatment to a minimum.

During the past two years three different therapeutic programs have been used. The changes have resulted from clinical experience as well as experimental results on the action of streptomycin on type b *H. influenzae*.

*Results of Treatment.* In the first twelve patients, treated according to our first program, streptomycin was used as the only therapeutic agent after admission to Babies Hospital unless it became evident from the poor response that amplification of this treatment was indicated. However, all patients with the exception of No. 12 had previously received sulfadiazine. All of the patients received streptomycin alone either throughout the period of treatment or for four days before the addition of other agents. From analysis of this group it is evident that recovery was prompt in the eight patients in whom the infection was mild or moderately severe, as judged by the concentration of sugar in the spinal fluid before treatment, as well as by clinical signs. On the other hand those with severe meningitis were not cured with streptomycin.

In three of these patients in whom streptomycin failed physical signs of chronic meningitis were present, and the concentrations of sugar in the spinal fluid were below 15 mg. per 100 cc. The prognosis for com-

plete recovery would be uncertain under any known treatment regimen. The disease of the fourth patient (case 12) in this group ran a fulminating course, since he was reported to have been up and well twenty-four hours prior to the institution of streptomycin therapy. On admission he was in a semi-comatose state and the level of sugar in his spinal fluid was only 6 mg. per cent. In our experience, such a patient could be expected to recover promptly under treatment with rabbit antiserum and sulfadiazine in adequate quantities. In two of these patients the unsatisfactory response led to the addition of type specific antiserum after four days of streptomycin treatment. In only one of these, case 12, was *H. influenzae* cultivated from the spinal fluid at the time antiserum was added, but in the other the worsening of the clinical condition and persistence of a low concentration of sugar in the spinal fluid demanded the use of additional therapy. In case 12, in which infection was early, *H. influenzae* was grown from all specimens of spinal fluid withdrawn during streptomycin administration. The organism cultivated from the spinal fluid twenty-four hours after the initiation of treatment with this antibiotic was found to be resistant to 1,000 units of streptomycin per cc.; 100 per cent of the bacterial population showed this degree of resistance. After the addition of antiserum and sulfadiazine, recovery was prompt and complete. The other patient, who received antiserum and sulfadiazine after four days of streptomycin therapy, exhibited evidence of serious cerebral damage. The two patients who were treated with streptomycin without additional therapy succumbed to the infection. In one the infection continued because the organisms which persisted were resistant to streptomycin. The other patient appeared to be improving by clinical standards; the spinal fluid became sterile and its chemical constituents normal. At necropsy a large

subarachnoid abscess containing *H. influenzae* was found.

The failure of streptomycin alone to cure any of the four patients with severe meningitis led to the second change in our therapeutic program. Only patients with initial spinal fluid sugar concentrations significantly above 15 mg. per cent were to receive streptomycin alone; those with concentrations at or below this level would receive all three therapeutic agents, streptomycin, sulfadiazine and specific rabbit antiserum initially. This therapeutic program has proved successful.

Table iv summarizes our results, already reported, of treatment\* of the first twenty-five patients.<sup>11</sup> In twelve patients already discussed the first therapeutic program was followed and in subsequent severe infections plan two was instituted. A larger experience continues to show prompt and complete recovery following use of streptomycin alone in those patients whose original spinal fluid sugar concentrations are significantly above 15 mg. per cent.

TABLE IV  
SUMMARY OF TREATMENT OF TWENTY-FIVE PATIENTS

No Patients Treated	Severity of Infection	S.M. Alone			Serum after 4 Days of S.M.			S.M. after Unsuccessful Serum and Sulfa			S.M. Serum Sulfa Initially		
		R	S	D	R	S	D	R	S	D	R	S	D
13	Mild or average	12	...	...	...	...	...	1	...	...	...	...	...
8	Severe chronic	...	2	...	2	...	...	1	1	1	1	...	...
4	Severe early	...	...	1	...	...	...	...	...	...	3	...	...

S.M. = Streptomycin  
R = Recovered  
S = Survived  
D = Died

Total R S D  
19 3 3

*Origin and Nature of Resistant Type b H. Influenzae to Streptomycin.* The proof that emergence of resistance of the strain was the cause of failure in two of these patients and

\* The streptomycin used for treatment of patients and experimental studies was supplied by E. R. Squibb and Sons.

in one patient with epiglottitis and bacteremia due to this organism, led to a study of the mechanism of resistance.

In order to explain these failures the strains isolated before streptomycin therapy from ten of these patients, treated according to first therapeutic program, were studied for evidence of fundamental differences between the group from patients in whom streptomycin failed and those from the patients who were promptly cured. In addition experiments were designed to determine the origin and nature of the resistant organisms which made up either 100 per cent or an appreciable part of the population grown from three of these patients during unsuccessful streptomycin therapy.

The routine *in vitro* sensitivity tests, which examined populations varying approximately from 1 million to 1,700 million organisms, failed to reveal a significant difference among the strains isolated from these ten patients prior to streptomycin treatment. Moreover infections produced in mice with the original strains, which later became resistant in patients during streptomycin treatment, exhibited marked sensitivity to streptomycin action. While neither the standard *in vitro* sensitivity test nor the mouse test applied to the cultures isolated before treatment of the patients with streptomycin could detect a difference between the strains from cases in which streptomycin was promptly effective and those from patients in whom resistance of the strain developed, when these procedures were applied to the same strains which continued to grow from the spinal fluid after treatment, they served as a good index of efficiency of treatment. Growth was easily demonstrable in 1,000 units of streptomycin per cc. and it was impossible to protect mice against such modified strains with doses as high as 5,000 units per mouse.

Therefore, enormous populations of each of the ten strains (142 to 522 billion) were

examined by a procedure which could demonstrate the presence, even in very small numbers, of organisms resistant to 1,000 units of streptomycin per cc. Certain factors learned from patients in whom streptomycin failed directed us to this approach. When emergence of resistance of the strain was responsible for therapeutic failure a relatively small inoculum of the culture from the spinal fluid grew on Levinthal agar containing 1,000 units per cc. of streptomycin. In one patient 100 per cent of the population of the culture grown from the spinal fluid withdrawn twenty-four hours after beginning streptomycin therapy, showed resistance to 1,000 units per cc. This concentration was so rapidly bactericidal for sensitive organisms *in vitro* that it was possible to examine 15 to 30 billion organisms in each pour plate of Levinthal agar containing 1,000 units of streptomycin per cc. without inhibiting growth of the resistant organisms as a result of accumulation of end products of bacterial metabolism; sensitive organisms were killed before they had a chance to reproduce. All colonies growing under these circumstances were resistant to 1,000 units of streptomycin per cc. The details of the test have been reported.<sup>9</sup> Table v lists the results of the ten strains.

Strains, 1, 2 and 3 were isolated from patients in whom streptomycin therapy failed because of emergence of resistance of the strain. The organisms grown from these patients before streptomycin therapy were sensitive according to conventional methods, whereas after a period of treatment of one, twenty-one, and three days, respectively, they grew in a concentration of streptomycin of 1,000 units per cc. Strain 4 was cultivated from a patient who improved at first and whose spinal fluid became sterile and normal by all standards but who died from pressure changes secondary to a large subdural abscess. The other six strains were grown from spinal fluid of patients who were

cured promptly by streptomycin. Again it should be emphasized that the tests described were applied in all instances to cultures isolated from patients before the start of streptomycin therapy.

TABLE V  
INCIDENCE OF RESISTANT SURVIVALS IN LARGE BACTERIAL  
POPULATIONS SEEDED IN LEVINTHAL AGAR CONTAINING  
1,000 UNITS OF STREPTOMYCIN PER CC.

Patient and Strain	Total Organisms Examined, Billions	Organisms Examined Per Plate, Billions	Colonies Total Survival	*Incidence of Resistant Colonies	Clinical Results
1.	381	25.4	57	1:6.7 billion	Failure
2.	142	14.2	23	1:6.2 billion	Failure
3.	301	30.1	26	1:11.5 billion	Failure
4.	423	29.2	32	1:13.2 billion	Failure
5.	253	25.3	20	1:12.6 billion	Recovered
6.	522	34.8	474	1:1.1 billion	Recovered
7.	188	18.8	18	1:10.4 billion	Recovered
8.	256	25.6	172	1:1.5 billion	Recovered
9.	166	16.6	12	1:13.8 billion	Recovered
10.	284	28.4	37	1:7.7 billion	Recovered

\* Ratio of resistant colonies to total population cultures.

It is seen that all ten cultures studied before exposure to streptomycin contain a minute fraction of members (expressed by the ratios in the column "Incidence of Resistant Colonies") which can grow in the presence of 1,000 units per cc. of the antibiotic. These ratios seem to bear no relationship to the tendency exhibited by a strain to emerge resistant during treatment of the patient. In fact, two of the strains, Nos. 6 and 8, cultivated from patients in whom streptomycin was promptly successful in eliminating the infection, showed a greater prevalence of resistant members than those which later emerged resistant during treatment.

The results demonstrate that the emergence of resistance is a selective process; the

sensitive members are killed, permitting the resistant organisms to declare themselves. When patients are treated according to the program described the size of the bacterial population is the most important single factor among those which determine the potentialities of a strain to exhibit this degree of resistance during treatment of a patient or in the test tube. However, when streptomycin is administered only by the intramuscular route, relatively small populations in the spinal fluid, when exposed to the low concentrations of streptomycin which are present in spinal fluid, will exhibit resistance of a significant but lesser degree.

These resistant variants apparently present in large populations of all sensitive strains of *H. influenzae* have been proven to originate from mutations.<sup>12</sup> Therefore, we can expect the continuous random occurrence of resistant mutants in patients if the disease is sufficiently severe or, in other words, if the bacterial population is large enough. The rate of occurrence of the resistant mutants did not differ significantly among the ten strains.<sup>12</sup> Therefore, the emergence of resistance of the strains in the three patients in whom streptomycin failed, cannot be explained on a greater frequency of occurrence of mutations. The resistant trait is transmitted unchanged in degree through many generations. Therefore, the appearance of a few mutants in a patient during treatment can lead to a serious infection which is uninfluenced by streptomycin. Moreover the persistence of resistant organisms in the nasopharynx of patients whose strains emerged resistant during streptomycin treatment constitutes a significant public health problem. In one streptomycin-treated patient followed at intervals for one year after recovery from meningitis all of the cultures of *H. influenzae* isolated from his nasopharynx showed resistance to 1,000 units of streptomycin per cc.

A fraction of the mutants which are resistant to streptomycin exhibit nutritional requirements different from the parent strain. There are even different nutritional needs among members of this minority. The results suggest that some may differ so greatly from the parent strain that normal Levinthal agar, an ideal medium for the majority group, is inadequate for their growth. This raises the question whether our failure to grow organisms from some patients is explained on a nutritional basis. Three patients with severe meningitis treated with streptomycin alone failed to improve clinically, the concentration of sugar in the spinal fluid remained low and in one a large number of gram-negative bacilli were seen on stained smear, but the cultures showed no growth. Following the institution of rabbit antiserum and sulfadiazine recovery was prompt.

It is of great significance therapeutically that the mutants, resistant to streptomycin,<sup>13</sup> are in general sensitive to sulfadiazine. As a result of this evidence our third therapeutic policy was instituted. Except for infants under six or seven months of age, patients with signs of severe meningitis are now treated with sulfadiazine and streptomycin. Those with milder disease will continue to receive streptomycin alone; the young infants with severe meningitis will receive all three therapeutic agents, streptomycin, sulfadiazine and specific rabbit antiserum. Three patients with manifestations of severe meningitis have been successfully treated with sulfadiazine and streptomycin used simultaneously from the beginning.

#### SUMMARY

A larger experience and more time for long term evaluation of physical and mental development are needed before final statements can be made concerning the results of treatment of *H. influenzae* infections. Certain facts are evident, however.

In patients in whom the infection is mild or moderately severe, according to the criteria previously described, either streptomycin alone or sulfadiazine in conjunction with specific rabbit antiserum can be expected to cure 100 per cent of them. A small fraction can be cured by sulfadiazine alone.

When manifestations of severe infection are present in patients in whom it is evident from the history that the onset of the meningitis can be dated within a few days, the results suggest that a choice may be made between two therapeutic programs, the combined action of sulfadiazine with either streptomycin or type b *H. influenzae* antiserum. Experience with the latter regimen is so extensive that one can predict complete recovery in virtually 100 per cent of these patients. The use of the former program, simultaneous use of sulfadiazine and streptomycin, is still too limited to recommend it with assurance in this group, though its success is anticipated. Patients whose infections have progressed to the severe state despite the use of sulfonamides cannot be considered suitable cases for treatment with sulfadiazine in conjunction with streptomycin; the presence of sulfadiazine resistant *H. influenzae* in significant numbers may prevent these agents from eliminating the meningeal infection. Moreover a longer period of study on the toxic effect of streptomycin on the central nervous system is necessary before it can be recommended as the treatment of choice for this group even if it proves to be equally effective.

Those patients with severe meningitis and a history which suggests that uncontrolled meningitis has been present for a week or more or who show signs of chronic meningitis with or without manifestations of localized cerebral injury should receive sulfadiazine, streptomycin and specific rabbit antiserum simultaneously. The latter program can be expected to reduce the risk of failure to a minimum since it combines the action of

three antibacterial agents which exert their destructive influences through three different mechanisms. Members of the population resistant to one can be attacked by another or both the others. The difficulty in determining the time of onset of meningitis in young infants under seven months of age, because of failure of these infants to exhibit signs of meningeal infection until several days after onset, together with the still high mortality rate in this group, have led us to recommend the use of sulfadiazine, streptomycin and specific rabbit serum initially for these infants. It is in this severest group that the addition of streptomycin to sulfadiazine and specific antiserum can be expected to reduce the 20 per cent mortality which resulted from the combined use of the last two agents.

The use of streptomycin alone or in conjunction with sulfadiazine is justifiable only when laboratory facilities permit evaluation of severity of infection and progress of recovery. The need for bacteriologic methods which can detect small numbers of viable organisms and evaluate sensitivity of any culture grown from the spinal fluid, is of paramount importance.

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# Treatment of Tularemia with Streptomycin\*

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STREPTOMYCIN approximates the ideal therapeutic agent for tularemia. Multiplication of *Bacterium tularensis* is prevented by a drug concentration of 0.4 microgram per cc., and the average virulent strain is killed *in vitro* by exposures to concentrations of 0.4  $\gamma$ /cc. for two hours, of 1  $\gamma$ /cc. for thirty minutes, and of 2  $\gamma$ /cc. for eight minutes.<sup>3</sup> This high degree of sensitivity of the causative agent to the antibiotic permits effective therapy of the experimental disease caused by 10 to 100 multiples of the MLD in totally non-resistant rodents. In addition to Heilman's<sup>1</sup> report there are other excellent, and somewhat more quantitative, studies on streptomycin therapy of the experimental disease, performed during the war, that are either unpublished at this time or available only in abstract. This is unfortunate, for only those who are familiar with these or similar data can realize how little streptomycin is required to prevent certain death in highly susceptible and wholly non-resistant animals.

Single doses of 10  $\gamma$ /Gm. body weight protected 92 per cent of mice against simultaneous challenge with 15 to 20 MLD of a strain of maximal virulence. When therapy was delayed for seventy-two hours after this challenge dose the minimal quantity which effected 80 per cent survival was 10  $\gamma$ /Gm. every three hours for ten days.<sup>2</sup> For comparison, a calculation from data presented in Heilman's first protection test shows that approximately 7  $\gamma$ /Gm. every three hours for ten days protected all of fifteen mice when therapy was de-

layed for seven hours after challenge with 32 LD<sub>50</sub> doses. In other work the total ED<sub>50</sub> dose (median effective dose, sparing 50 per cent of all animals) administered in four equal portions every two hours, the first portion at time of challenge with 50 LD<sub>50</sub> doses of the same virulent strain, averaged 350 $\gamma$  for the 20 Gm. mouse, or 17  $\gamma$ /Gm.<sup>3</sup>

The implications in the above, and in other similar data, seem reasonably clear that streptomycin therapy of tularemia in man should be at least as effective, if not more so, at equivalent concentrations and administrative periods than it is in mice, hamsters, and guinea pigs whose recoveries are solely dependent upon streptomycin alone, for the average human develops so great a degree of natural resistance after infection that clinical and histologic aspects of the disease soon exhibit subacuteness and chronicity, and the mortality rate is characteristically low, averaging about 6 per cent. The purpose here is to learn by examination of available clinical data how well the early collective experience has kept pace with expectations.

Quantitative information about the results of therapy was obtained from thirty-seven patients, including one that died, giving a fatality rate of 2.7 per cent for the series. The items of importance in the composition of the group are an average age of thirty-six with extremes of ten and seventy-nine, and nine individuals of fifty-one years or above; ten examples of the typhoidal clinical type, an incidence of 27 per cent; fourteen patients with tular-

\* From the Department of Bacteriology, College of Medicine, University of Cincinnati, and the Cincinnati General Hospital.



emic pneumonia, a frequency of 37.8 per cent, including two with bilateral pneumonia and three with accompanying large pleural effusions. Thus the group was composed of infections of considerably greater average severity than would have been encountered by a random selection. The time of onset of therapy ranged from the second to the one hundred twenty-third days of disease, with the average on the twenty-second day. The usual mode of administration was by intramuscular injection every three hours, occasionally every four hours. A few dangerously ill patients received part of the total amount by continuous intravenous or subcutaneous drips. The periods of administration varied from two to seventeen days, and the total dosage per patient varied from 0.64 to 29.5 Gm.

All published reports<sup>4-15</sup> as well as all private communications received to date, were in agreement that streptomycin modified favorably the course of the disease, usually promptly and often dramatically. The only apparent exceptions were three patients who were treated during the eleventh, seventh and third months of disease.<sup>13</sup> Otherwise the observed objective evidences of improvement were lowered temperature, reduction in diameters of buboes and restoration of mental clarity, usually preceded or accompanied by equally prominent subjective changes, notably relief from headache, sense of prostration, mental depression, arthralgias and myalgias, and lessened pain in primary lesions and in buboes. If pneumonia was present, the additional diminution or disappearance of cough and the reductions in pulse and respiratory rates created a dramatic turn of events. Regardless of the stage of disease at which therapy was instituted the temperature usually fell to normal within seventy-two hours, a highly significant change for the eighteen patients who were given treatment before the fifteenth day of

disease, and especially so for the fourteen patients who had tularemic pneumonia. In one case the distressing sequel of serial suppuration of lymphadenopathies was promptly halted.<sup>6</sup> Early treatment did not prevent all suppurative lymphadenitis though it did reduce the frequency to a new low level. Primary lesions that were in the non-ulcerated papular stage at the onset of therapy usually healed without ulceration, and in about one-third to one-half of the usual healing time.

The average results of therapy are shown in Table 1, in comparison with means obtained from untreated patients and from a group that was treated with hyperimmune serum, the latter probably representing the best results obtainable with serum therapy.<sup>7</sup> The extraordinary therapeutic effectiveness of streptomycin is not adequately reflected by the figures presented. This is apparently due to the inclusion in this small series of three patients who were not treated until the seventy-ninth, one hundred third, and one hundred twenty-third days of disease, respectively. Nevertheless a duration of disease of less than two months, and a therapy-to-recovery interval of considerably less than forty-six days are new low constants for tularemia, exceptionably remarkable in view of the late average time of onset of therapy, the twenty-second day of disease. Averages that were more in harmony with the usual clinical experience were obtained by arbitrarily excluding from computations the data from the three late treated patients. These figures, shown within parentheses, are more representative of the results of treatment during the severe acute phase of the disease, and probably foreshadow more accurately the results to be secured eventually by proper analysis of a suitably large series.

Five patients were desperately ill when therapy was initiated on the third, thirteenth, twenty-fourth, twentieth, and fifth

TABLE I

COMPARISON OF MEANS FROM THE CONTROL AND HYPERIMMUNE SERUM TREATED GROUPS  
WITH AVERAGES FOR THE STREPTOMYCIN TREATED GROUP

	Untreated N = 542	Hyperimmune Serum N = 54	Streptomycin	
			N = 36	(N = 33)
Duration of:				
Disease, months.....	3.78	2.15	1.85	(1.50)
Disability, months.....	3.12	1.87	1.91	(1.59)
Adenopathy, months.....	3.50	1.78	2.03	(1.73)
Fever, days.....	30.6	28.9	29.7	(23.7)
Bed days.....	46.8	23.3	27.5	(23.3)
Primary lesions, days.....	40.6	30.9	27.6	(27.7)
Day of disease therapy was begun.....	.....	17	22	(14)
Suppurative adenitis, per cent.....	56	26.5	20	
Mortality, per cent.....	6	3.3	2.7	
Therapy-to-recovery interval, days.....	.....	46	38	(37)

days of disease, respectively. All exhibited the typhoid state, and two had non-remittent fever at high levels, a symptom combination which in the past has usually been followed by death within seven days. Transitions from the highly febrile, incontinent, stuporous state to one of cheerful competence with sustained progressive improvement were effected within seventy-two hours by treatment of the first four patients. The fifth, a woman of fifty-five who had had signs of pneumonia by the second day of disease, and who had been delirious since the third day, was admitted late on the fourth day and died early in the sixth day despite treatment at the rate of 0.15 Gm. every three hours during the previous fifteen hours.

The duration of pulmonic exudates was measured in ten patients by means of serial chest films. The approximate times of appearance and disappearance of exudates are tabulated in Table II against the day of disease upon which therapy was initiated. Although sufficient accurate data are not available for comparison it is generally known that tularemic pneumonias resolve slowly and that exudates commonly persist

for two months and not infrequently throughout the third month of disease. Streptomycin therapy apparently effected a considerable reduction in the resolution time and, on the average, the less the interval between detection of pneumonia and institution of therapy the shorter was the period of repair.

TABLE II  
THE DURATION OF PULMONARY EXUDATES IN TEN PATIENTS  
WHO WERE TREATED WITH STREPTOMYCIN

Approximate Day of Disease Pneumonia Appeared	Day of Disease Therapy Instituted	Approximate Day of Disease Exudate Disappeared
8	8	28
7	11	21
4	11	62
6	13	31
1	17	29
4	18	41
17	20	38
10	22	51
4	24	97+
13	79	144+

Although there is unanimous agreement so far that streptomycin therapy is highly effective in acute tularemia there is obvi-

ously no widespread appreciation of just how effective it really is, nor any agreement about dosage requirements. Perhaps the total experience is too small to expect it. Two dosage plans are discernible in published reports. In one the dosage varies from 1 to 3 Gm. per day for from seven to ten or twelve days, and occasionally longer. Although this "playing safe" policy makes the patient and the physician feel vastly better within a day or two it contributes nothing else beyond a reaffirmation that the antibiotic is effective in this disease. The other shows early attempts to determine the minimal and safest, most efficient dosage range and, through its rewarding, increased insight into disease processes, to lay the groundwork for skilful and economic management. It may not be without significance that those who are most familiar with the disease are using the smaller dosages.

Peterson and Parker<sup>9</sup> secured a brilliant result in a pneumonic patient with temperature peaks reaching 104.2°F. or more daily, using a total of 1.9 Gm. In fact, the dramatic change within twenty-four hours to the afebrile and asymptomatic state was effected by the administration of 0.9 Gm. at the rate of 0.05 Gm. every three hours, for two and one-fourth days, beginning on the eleventh day of disease. The additional 1 Gm. was administered at the same rate, starting three days after cessation of the first amount. Their considered judgment in this case was, "It is doubtful whether the latter series was necessary. The patient had been afebrile for 3 days when the second course was started; he was showing steady improvement, and the subsequent illness did not indicate that the additional streptomycin had been beneficial."

Abel<sup>5</sup> reported an equally satisfactory response in a man with the ulceroglandular type without pneumonia but with large buboes. Two Gm. of streptomycin were

administered at a rate of 0.166 Gm. every four hours for two days, starting on the eighth day of disease. He commented, "Inasmuch as the clinical use of streptomycin in tularemia is scant, the yardstick of dosage has not been established. On this basis, only two million units were administered to this patient and the results were just as good as in the previous patient who received 7 million units."

The first seven patients reported by Foshay and Pasternack<sup>4</sup> showed equally satisfactory clinical responses following administration of a usual total dose of 1.2 Gm., with a maximal of 1.76 Gm. One was in the desperately ill classification and another had tularemic peritonitis with the abdominal cavity distended with infected fluid. One experienced a late, recurrent lymphadenitis with rapid necrosis and formation of a subpectoral abscess. A later attempt<sup>7</sup> to approximate a minimal, safely effective dosage, made in another desperately ill patient with bilateral tularemic pneumonia, showed that even an infection of maximal severity was controllable by streptomycin administration at a rate of 0.5 Gm. per day, and that treatment for two or three days at this rate might be expected to be a reasonable maximal requirement. Further evidence to support this probability can be found in the report and in the administration chart of the patient treated by Cohen and Lasser,<sup>8</sup> another desperately ill patient in whom the dramatic turn of events was accomplished by the administration of 0.5 Gm. per day. It is not clear that the subsequently doubled rate was necessary or beneficial. After the dramatic fall in temperature and restoration to consciousness and to a state of progressive improvement each of these latter patients showed irregular, low to moderate fever during the period of earliest favorable changes in the pulmonic exudates. The chart referred to indicates that the period of fever coincided with

specific *in vivo* agglutinin absorption, and that it was, therefore, a consequence of effective therapy and not an indication for more treatment, as they correctly judged.

Untoward reactions have been few. Two patients who were receiving 0.1 Gm. every three hours experienced dermal rashes, one with an accompanying sharp rise in temperature.<sup>13</sup> An unreported patient had a dermal rash, accompanied by a sharp rise in temperature and muscular cramps in the calves, on the eighth day of administration at a rate of 0.15 Gm. every three hours for a total of 9.3 Gm. Subsequent observation at six weeks after discharge from hospital disclosed persisting vertigo and tinnitus. Although many patients showed a small rise in temperature within eight hours of institution of therapy the associated brief intensification of disease symptoms, in the few cases in which it was detectable at all, was negligible and trifling. The only patient to experience the analogue of the Herxheimer reaction was the previously reported one with the infected, massive peritoneal exudate.<sup>4</sup>

#### COMMENT

An important practical result of the healing without ulceration of papular primary lesions was that it prevented secondary pyogenic infection of ulcers and, in consequence, greatly reduced the frequency of suppuration of buboes. If a few physicians and patients could have been dissuaded from incising or needling early, unbroken, primary papules it is not unlikely that the incidence of suppurative adenitis in this series would have been lowered still further. It is apparently not widely appreciated that these secondary infections, usually by hemolytic staphylococcus aureus, and especially if the lesions become dry and seal over, appreciably increase the frequency of suppurative adenitis. Indeed, adequate local and, if need be, appropriate systemic ther-

apy to control existing secondary pyogenic infections of ulcers and buboes would contribute materially to lower the bubo suppuration rate. Not all re-enlargements of buboes are due to secondary infection but should a typically effective streptomycin response be followed by recurrence of low to moderate fever, with gradual re-enlargement and increasing tenderness of previously shrunken buboes, it might be remembered that the likelihood of secondary infection is considerably greater, based on experience to date, than a reactivation of the tularemic process. This held true throughout many years of observation of the effects of serum therapy, and it is already becoming evident following streptomycin therapy.

The three patients in the second group reported by Howe, Coriell and associates<sup>13</sup> stand out in marked contrast to all others since therapy administered at the rate of 0.1 Gm. every three hours for from three to seven days failed to induce appreciable immediate favorable changes, and played at most a doubtful part in the recoveries that eventually followed at two, four and three months, respectively, after cessation of therapy. These patients had weathered fairly mild acute phases of the disease and, at the time of treatment, were suffering frequent intermittent attacks of low to moderate fever associated with sense of prostration, great fatiguability and, in one case, generalized enlargements of lymph nodes. The association of transitory *in vivo* specific agglutinin absorptions with recurrent exacerbations of symptoms characteristic of tularemia makes any other cause for the chronic illnesses highly improbable. Considerations of the mild character of the acute phases, the previous prophylactic vaccinations, or the late stages of disease at which therapy was initiated have suggested no plausible reasons for the state of refractoriness to therapy. One might suspect that

the locations, presumably intracellular, in which the surviving bacteria were held in inadequate or impermanent bacteriostatic equilibrium were impermeable to streptomycin at the prevailing concentrations. In any event it seems more probable that the fundamental abnormality in such cases is a defect in the individual's defense apparatus rather than in the activity of the antibiotic. Similar examples have been observed among unvaccinated laboratory personnel.<sup>16</sup> The clinical courses and the responses to streptomycin therapy of these uncommonly seen examples of chronic tularemia resemble those of subacute or early chronic brucellosis so very closely that it suggests some common causative feature in the respective host-parasite relationships.

Although it seems that most physicians are using far larger amounts of streptomycin than are really necessary for their patients, it is in relation to this very matter of suppurative adenitis that the effect of total quantities larger than 2 or 3 Gm. per patient might be studied much more, particularly in patients with buboes with diameters of 5 cm. or more at the time treatment is initiated. Buboes of this size seldom escaped eventual suppuration in the pre-streptomycin days. Several patients in this series had liquefaction necroses after total dosages of 1 to 3 Gm. On the other hand another, who had no nodes palpable when therapy was started on the fifteenth day of disease, received 1 Gm. per day for seven days, and then developed rapid re-enlargement and liquefaction of an axillary node which required drainage on the tenth day after cessation of therapy. Others who received 6, 8 or even 20 Gm. of streptomycin still have large nodes, some tender and fluctuating in size, whose ultimate outcome cannot be predicted. Since buboes that may have disappeared entirely with or without treatment are known to re-enlarge and to progress rapidly to liquefac-

tion up to six or twelve or even to thirty months after recovery there can be no assurance of success but it seems justifiable to try larger dosage to see if this will further reduce the incidence of suppurations. The crux of the matter seems to be the difficulty in distinguishing between the results of persisting or of mixed infection and the consequences of irreversible tissue damage that may have been inflicted prior to the onset of therapy.

The patient with the typhoidal clinical type, often with tularemic pneumonia but clearly not in the desperately ill category, is the one who is presently receiving the largest therapeutic doses. Although it may seem contrary to expectations based upon experience with other infections it is precisely this type of tularemic infection which responds dramatically to the smaller total dosages of 2 or 3 Gm. administered over a four to six-day period. The importance of treating infections with high initial concentrations of bacteriostatic or bactericidal agents is not minimized; the sensitivity of *Bacterium tularensis* to streptomycin is simply so high that adequate initial blood concentrations are easily achieved by the above recommended dosage which, furthermore, is much less apt to induce hypersensitivity or other toxic or undesirable drug reactions.

The problem of the fulminant case, the one person out of approximately each thousand who reacts to invasion with no more effective resistance than does the rabbit, and who similarly dies between the fifth and tenth days of disease, is one of early diagnosis. The amazing effectiveness of streptomycin in totally non-resistant laboratory animals justifies the expectation that these deaths could be prevented if treatment could be given early enough.

#### SUMMARY

There is uniform agreement that streptomycin is an extremely effective thera-

peutic agent in tularemia. Although the experience is too small to permit formulation of an optimal dosage, no evidence has yet appeared that either (1) 0.5 Gm. per day for two days followed by 0.25 Gm. per day for four days or (2) 0.5 Gm. per day for six days is not adequate dosage for the case of usual severity, with or without tularemic pneumonia.

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# Treatment of Urinary Tract Infections with Streptomycin\*

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THE earliest reports indicated that streptomycin effectively inhibited the growth of most of the gram-negative bacteria responsible for infection of the urinary tract.<sup>1,2,3,4</sup> Clinical studies have indicated the importance of anatomical conditions prevailing in the genitourinary tract and the bacterial flora producing infection as factors influencing the results obtained from treatment with streptomycin.<sup>5,6,7,8,9</sup> The purpose of this report is to review briefly the basic pharmacological and bacteriological data of direct importance in the treatment of urinary tract infections and to summarize the experience at the Massachusetts Memorial Hospitals as illustrative of the present state of our knowledge concerning the use of this chemotherapeutic agent in the management of these infections.

## PHARMACOLOGY

Streptomycin administered intramuscularly produces maximum blood levels within one to two hours after injection and appears rapidly in the urine during the first hour after injection. After a single dose of streptomycin the urinary excretion of the drug is greatest during the four hours following injection corresponding to the period of highest blood levels and continues over a twenty-four to forty-eight hour period.<sup>10,11,12</sup> The rate of renal excretion of streptomycin is thus considerably slower than that of penicillin. One hour after injection 60 per

cent of a given dose of penicillin can be recovered from the urine and excretion is almost complete within four hours whereas 20 to 30 per cent of a single dose of streptomycin is excreted later than four hours after administration.

The concentration of streptomycin in the urine is related to the dose of the drug, urine volume and renal function. Considerable variation exists in the total amount and in the concentration of streptomycin excreted in the urine. Sixty to 80 per cent of the dose administered usually appears in the urine and on dosage schedules of 2 to 4 Gm. per day concentrations of 25 to 5,000 micrograms per cc. of urine may be obtained. In our cases in which it has been feasible to limit the daily fluid intake to 2,500 cc. and with a daily dose of 1 Gm. of streptomycin a minimum urine level of 100 micrograms per cc. has been present almost uniformly. Two Gm. of streptomycin daily usually has insured a urine level of 250 micrograms per cc. The concomitant use of oral alkali with streptomycin has not produced any significant effect on the urinary excretion of the drug. Several investigators have observed patients with advanced renal disease who manifest decreased renal excretion of streptomycin with low urine levels and markedly increased serum levels.<sup>8,11</sup> We have not observed this phenomenon, but in occasional instances it may be of therapeutic importance by preventing urine levels adequate for bacter-

\* From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

icidal action. In connection with the treatment of renal and urinary tract infections the work of Adcock and Hettig is of interest in which postmortem assays were performed on the organs of two patients receiving streptomycin and the amount of the drug in renal tissue was found to be approximately twice that present in the serum whereas considerably smaller amounts were present in the lung and heart muscle.<sup>13</sup>

### BACTERIOLOGY

The bacteria which occur most commonly in urinary tract infections are gram-negative bacilli of which *Escherichia coli* and *Aerobacter aerogenes* are most frequently isolated. Gram-positive cocci may also be present, and of the streptococci the non-hemolytic enterococcus group and alpha hemolytic streptococci are more common than beta hemolytic types. The relative frequency of various groups of bacteria in the series reported by Braasch<sup>14</sup> and by DeBakey and Pulaski<sup>15</sup> is cited in Table 1 for

TABLE I  
FREQUENCY OF OCCURRENCE OF BACTERIA IN URINARY TRACT INFECTIONS

Organism	Braasch <sup>14</sup>	DeBakey Pulaski <sup>15</sup>	Mass. Mem. Hosp. Series
Total cases.....	200	680	75
<i>E. coli</i> .....	84	132	51
<i>A. aerogenes</i> .....	26	170	17
<i>Staphylococci</i> .....	28	58	2
<i>S. fecalis</i> .....	8	83	12
<i>Proteus sp.</i> .....	6	115	18
<i>P. aeruginosa</i> .....	...	70	12
<i>B. mucosus</i> .....	...	32	8
<i>H. influenzae</i> .....	...	...	1
Mixed infections..	17	...	33

comparison with our own cases. Urinary tract infections may occur with a single organism or a mixed infection with several types of bacteria may be present. The frequency with which groups of organisms different from those originally present appear

during treatment suggests that mixed infections may be more frequent than previously supposed and that infections which are apparently caused by a single group of bacteria may in some instances represent the predominance of one group which when suppressed allows other types to appear in numbers capable of detection. This phenomenon was observed in 31 per cent of our cases. Gram-positive cocci insusceptible to streptomycin occasionally appear in the urine following suppression of gram-negative bacilli and the appearance of gram-positive cocci in the sputum, nose and throat in some instances followed by fulminant infections must be remembered as a possible complication of streptomycin therapy.<sup>16</sup>

Most of the organisms encountered in urinary tract infections are susceptible *in vitro* to the concentration of streptomycin obtainable in the urine although cultures which are naturally resistant are encountered. These are relatively infrequent except for *Pseudomonas aeruginosa* and *Streptococcus fecalis*. Published reports and our own experience indicates that about 75 per cent of the cultures of *E. coli*, *A. aerogenes* and *Proteus sp.* are sensitive to a concentration of streptomycin of twenty micrograms or less per cubic centimeter. All of the fourteen cultures of *Proteus sp.* we have tested have been sensitive to less than 20 micrograms of streptomycin per cc. A concentration of streptomycin of over 100 micrograms per cc. was required to inhibit two of nine cultures of *Pseudomonas aeruginosa* and six of twelve cultures of *Streptococcus fecalis*. Although *E. coli*, *A. aerogenes* and *Proteus sp.* are usually quite sensitive to streptomycin *in vitro*, Helmholz found that under the experimental conditions he employed urine containing less than 66 micrograms per cc. produced no interference with growth and that a concentration of at least 100 micrograms per cc. was necessary before



bactericidal effect on *Pseudomonas aeruginosa* and *Streptococcus fecalis* was observed.<sup>17</sup> Furthermore, the number of bacteria commonly present in urinary tract infections exceeds considerably the number employed under the experimental conditions of the *in vitro* sensitivity test and a large margin of safety is probably important in determining the urine level of streptomycin desired on the basis of the sensitivity of the organisms which are present. The decreased antibacterial effect *in vitro* of streptomycin when the pH of the culture medium is less than 7.0 is well known. Wolinsky and Steenken<sup>30</sup> noted a progressive decrease in antibacterial effect as the pH of the culture medium was decreased from 7.7 to 5.2 with the most marked diminution occurring between pH 6.6 and 5.9. No destruction of streptomycin occurs nor has any change been observed in its antibacterial activity in the presence of purulent or non-purulent exudates, serous transudates or normal tissue juices. The presence of procaine likewise produces no neutralization of antibacterial activity.

The ease with which bacteria develop resistance to the antibacterial action of streptomycin has been well demonstrated.<sup>18, 19, 20</sup> This phenomenon represents the primary factor limiting the therapeutic efficiency of this drug. The degree to which streptomycin resistance can develop is of a high order of magnitude. By successive transfer into media containing increasing concentrations of streptomycin cultures can be obtained of all of the gram-negative bacilli occurring in urinary tract infections which grow readily in the presence of streptomycin in concentrations of 25,000 to 50,000 micrograms per cc. This represents absolute resistance for therapeutic purposes. Bacteria recovered routinely from patients with urinary tract infections in which bacteriological cure has not occurred frequently possess this same order of resistance.<sup>21</sup> These organisms

do not differ significantly morphologically or in the biochemical reactions they produce from the original cultures from which they were derived although a change in pigment production and a reduction in rate of carbohydrate fermentation by staphylococci which have become streptomycin resistant *in vitro* has been noted.<sup>20</sup> No relationship has been observed between the sensitivity of bacteria to streptomycin and their response to other chemotherapeutic agents. Cultures which have become resistant either *in vitro* or *in vivo* to high concentrations of streptomycin manifest the same degree of sensitivity to penicillin and to sulfonamides as they did before exposure to streptomycin.<sup>20, 22</sup>

The rate at which streptomycin resistance develops may be quite rapid particularly when compared with the rate of the development of penicillin resistance. Employing the usual *in vitro* technic Knop<sup>23</sup> studied the development of resistance to streptomycin of cultures of *E. coli*, *A. aerogenes* and *Proteus* sp. which were sensitive to a concentration of 6 micrograms per cc. Seven transfers were sufficient to produce cultures resistant to 1,000 micrograms per cc. in some instances and all the cultures became resistant to this concentration of streptomycin in twelve to twenty-four transfers. The use of nutrient broth or urine as a culture medium did not produce any significant difference in these results except when *Proteus* sp. was grown in urine containing streptomycin. Bactericidal action occurred so readily under these circumstances that the development of resistant bacteria was difficult. A possible explanation for this difficulty is the ability of this organism to decompose the urea present in urine with formation of ammonia and production of an alkaline medium in which the activity of streptomycin is greatly enhanced. Cultures of *Pseudomonas aeruginosa* and *Streptococcus fecalis* developed streptomycin resistance more readily than the other bacteria tested.

## CLINICAL MATERIAL

A number of reports have appeared concerning the treatment of urinary tract infections with streptomycin.<sup>5, 9, 15, 21, 24, 26</sup> Seventy-five cases of urinary tract infections have been treated at the Massachusetts Memorial Hospitals.\* The published reports and our own cases may be divided into several clinical groups in which the effectiveness of streptomycin can be evaluated separately.

*Acute Pyelonephritis.* Eight patients with acute urinary tract infection with marked constitutional symptoms and signs have been treated. Seven of these patients showed dramatic clinical improvement with rapid decrease of fever, costovertebral angle tenderness, leukocytosis, and pyuria and improvement in renal function. In several instances this improvement was of value in preparation of the patient for surgery. With clinical improvement bacilluria has usually been temporarily reduced on the basis of quantitative measurements by the plate count method but in only one case did sterilization of the urine occur. Pyuria was decreased in six cases but disappeared in none. Control of bacteremia which frequently accompanies acute pyelonephritis may be of importance in producing a good clinical response.

*Pyelonephritis of Pregnancy.* Nine cases of pyelonephritis of pregnancy have been treated all of which have manifested symptoms and signs consistent with moderate or severe acute pyelonephritis rather than merely pyuria and bacilluria. Inasmuch as symptoms and fever commonly subside on a regimen of bed rest and administration of

\* The urological care of these cases was the responsibility of Drs. S. N. Vose and D. L. Anderson without whose cooperation these studies would not have been possible.

Streptomycin was provided by The National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman.

large volumes of fluid, evaluation of the rôle played by streptomycin in these cases is difficult. Six patients manifested an excellent clinical response with decreased pyuria and bacilluria and three of these showed sterilization of the urine. Pyuria almost disappeared in the three patients whose urine became sterile. Two of the three bacteriological cures relapsed within one month following discharge from the hospital but in both cases the bacteria isolated were sensitive to concentrations of streptomycin less than 32 micrograms per cc.

*Chronic Pyelonephritis.* Eighteen patients with urinary tract infections have been treated in which some anatomical obstruction to the free flow of urine has been present. Sterilization of the urine occurred in only three (17 per cent) of these patients. Fourteen cases of urinary tract infections have been treated in which no obstructive element could be found with urinary sterilization in eleven (79 per cent) of these patients. Pyuria responded more irregularly than bacilluria. Whereas bacilluria was frequently reduced temporarily in those cases in which bacteriological cure was not attained, pyuria frequently continued undiminished and in only eight of the twenty-nine instances of urinary sterilization in our entire series did pyuria cease. The response of mild urinary tract symptoms and low grade fever associated with chronic pyelonephritis was also quite irregular.

Calculi were present in eleven of our cases accompanied by *Proteus* sp. in seven instances. Clinical improvement was noted in nine patients who were experiencing acute exacerbations of chronic pyelonephritis but bacteriuria ceased in only three cases. Two of these underwent nephrectomy rendering it impossible to attribute bacteriological cure to streptomycin and the third patient developed recurrent bacteriuria four days after cessation of streptomycin therapy. It is worthy of note, however, that

*Proteus* sp. was eradicated from the urine and the urine became acid in all cases although other gram-negative rods persisted.

The importance of anatomical complications producing urinary stasis has been noted by others. Pulaski<sup>8</sup> reported four cases of calculi with two bacteriological cures both of which had simultaneous surgical removal of the calculi. Of twenty-six patients with calculi reported by DeBakey and Pulaski<sup>15</sup> only four showed improvement with no data being given concerning urinary sterilization. Harrell et al.<sup>26</sup> grouped cases as complicated and uncomplicated and noted good results in twenty-five of twenty-eight cases in the latter group as contrasted with four of twenty-four patients in the former group.

*Preoperative and Postoperative Use of Streptomycin in Relation to Genitourinary Surgery.* Streptomycin has been of value in controlling severe constitutional manifestations of acute infection of the urinary tract prior to surgery. The clinical response to streptomycin therapy of acute pyelonephritis occasionally with bacteremia has permitted extensive genitourinary surgery under much more favorable conditions than existed prior to chemotherapy. In situations in which sulfonamides are contraindicated, as in the presence of ureteral obstruction by stone, streptomycin is the chemotherapeutic agent of choice. When the circumstances for bacteriological cure are unfavorable due to the presence of obstruction, calculi, undrained abscesses or catheters, the development of bacteria resistant to streptomycin may preclude the usefulness of the drug during the postoperative period. When the main source of infection is to be removed as in nephrectomy this difficulty may to some extent be obviated. The clinical response to streptomycin of patients with abscesses associated with the genitourinary tract has been poor in the cases reported and in the three cases of perinephric infection

treated by us clinical improvement was obtained in only one patient who had undergone surgical drainage prior to institution of streptomycin. The use of streptomycin in the presence of localized accumulations of exudate affords bacteria an ideal opportunity for development of resistance by exposing them to concentrations of a chemotherapeutic agent inadequate to insure bactericidal action.

The use of streptomycin preoperatively or postoperatively in patients in whom urological indications demand catheter drainage has been uniformly disappointing. The indwelling catheter, suprapubic cystostomy or nephrostomy tube acting as a foreign body is accompanied by the development or introduction of bacteria resistant to streptomycin. Four patients who had sterile urine and who were to have urological procedures necessitating an indwelling catheter preoperatively were placed on a daily dose of streptomycin of 4 Gm. prior to insertion of the catheter. Within seven days urine culture of each patient revealed gram-negative bacilli which were resistant to a concentration of streptomycin of 5,000 micrograms per cc. In only a single case in our entire series was sterilization of the urine accomplished in the presence of an indwelling catheter. The use of streptomycin under these conditions should be limited to those patients manifesting severe, uncontrolled acute upper urinary tract disease or bacteremia associated with urinary tract disease.

Lower urinary tract infection with persistent pyuria is one of the troublesome and frequent complications of transurethral prostatic resection. In an effort to shorten the period during which pyuria and bacilluria were present ten patients were given streptomycin following transurethral resection of the prostate, five being given a daily dose of 1 Gm. and five a daily dose of 4 Gm. Decreased pyuria or bacilluria was not observed during or after streptomycin

therapy. The bacteria present prior to treatment in all cases were sensitive to a concentration of streptomycin less than 64 micrograms per cc. and those isolated after completion of treatment were resistant to concentrations of streptomycin over 10,000 micrograms per cc.

*Urinary Tract Infections Associated with Paraplegia.* Petroff and Lucas<sup>7</sup> reported thirty-five cases of urinary tract infection associated with paraplegia treated with comparatively small doses of streptomycin. In thirteen patients who had automatic bladders and were voiding without use of catheters sterilization of the urine occurred in nine cases but all became reinfected within four days. The treatment of twenty-two cases with indwelling catheters present resulted in urinary sterilization of ten patients for a period of one to two days but bacteria were again recovered from all patients within four days. Pulaski<sup>8</sup> reported bacteriological cure in three of eight paraplegics treated with a daily dose of streptomycin of 2.4 Gm. The patients in whom urinary sterilization was observed did not have suprapubic fistulas or residual urine. The largest series of 221 cases has been reported by DeBakey and Pulaski.<sup>15</sup> In patients in whom calculi were not present improvement was noted in 35 per cent of those treated. When calculi were present improvement occurred in only 11 per cent of patients treated and when undrained abscesses or cellulitis were present good results were observed in only 7 per cent of the patients treated.

*Acute Epididymitis.* We have treated two patients with acute epididymitis. One case occurred following dilatation of a urethral stricture and the other followed trans-urethral prostatic resection. Gram-negative bacilli persisted in the urine during streptomycin therapy but dramatic relief of pain with rapid reduction in scrotal swelling and tenderness occurred twenty-four hours

after institution of chemotherapy. Six other cases of epididymitis have been reported with similar good clinical results in three instances and failure in three patients in which surgical treatment was necessary.<sup>5,26,31</sup>

*Urethritis.* Streptomycin has not been used extensively in urethritis. *Neisseria gonorrhoeae* is quite susceptible to streptomycin *in vitro*.<sup>19,27</sup> Five cases of gonococcal urethritis have been reported with cure in all cases.<sup>15</sup>

#### BACTERIOLOGICAL FEATURES OF CLINICAL MATERIAL

Forty-two single infections and thirty-three mixed infections were present in our series. Infections with a single type of organism responded as well clinically as did

TABLE II  
BACTERIOLOGY AND RESULTS OF TREATMENT OF URINARY TRACT INFECTIONS

Type of Infection	No. of Cases	Good Clinical Result	Poor or Indefinite Response	Bacteriuria after Treatment	
				Present	Absent
Single organism...	42	27	15	20	22
<i>E. coli</i> .....	24	15	9	13	11
<i>A. aerogenes</i> ...	4	1	3	4	0
<i>Proteus</i> sp. ....	6	5	1	0	6
<i>P. aeruginosa</i> ...	4	3	1	2	2
<i>B. mucosus</i> ....	1	1	..	0	1
<i>S. fecalis</i> .....	2	1	1	0	2
<i>H. influenzae</i> ...	1	1	..	1	..
Mixed infections...	33	21	12	26	7
<i>E. coli</i> .....	27	15	12	20	7
<i>A. aerogenes</i> ...	14	9	5	8	6
<i>Proteus</i> sp. ....	12	7	5	2	10
<i>P. aeruginosa</i> ...	9	6	3	2	7
<i>B. mucosus</i> ....	7	3	4	3	4
<i>S. fecalis</i> .....	10	7	3	3	7
Total.....	75	48	27	46	29

those with mixed bacterial flora in the urine. Definite clinical improvement was observed in 64 per cent of the patients with each type of infection. However, sterilization of the

urine occurred in 52 per cent of the patients with a single type of infecting organism and in 21 per cent of those with mixed bacteriological flora. The overall recovery rate was 39 per cent. These results are in accord with those obtained in the 409 cases reported by Keefer et al.<sup>32</sup> The frequency with which each specific organism was eradicated from the urine is given in Table II. Infections with *E. coli*, *A. aerogenes*, *P. aeruginosa* and *S. fecalis* appeared to respond about equally well to streptomycin. *Proteus* sp. was present in eighteen cases of urinary tract infection. This organism disappeared from the urine in sixteen pa-

of streptomycin. Negative urine cultures have been obtained twelve hours after institution of therapy and all of our nineteen bacteriologic cures showed sterile urine at the end of forty-eight hours of therapy.

The streptomycin sensitivity of the bacteria present in the urine of the cases treated is presented in Table III. The only naturally resistant bacteria encountered were *P. aeruginosa* and *S. fecalis*. The six resistant cultures of *S. fecalis* required a concentration of streptomycin of 250 micrograms per cc. to inhibit their growth. Naturally resistant strains of both of these organisms are relatively frequent. Within the group of sensitive organisms no correlation was observed between degree of sensitivity and therapeutic success so that the isolation of an extremely sensitive organism afforded no information of prognostic value.

METHOD OF TREATMENT

The daily dosage of streptomycin employed by us has varied from 1 Gm. to 4 Gm. administered by the intermittent intramuscular method with time intervals of three or six hours between injections. The duration of treatment has been five to seven days in most cases. The average daily dose has been 1.5 Gm. given for an average of 7.9 days. The average total dose has been 11.6 Gm. Alkalinization of the urine with 2 Gm. of sodium bicarbonate or 2 Gm. of sodium citrate every four hours has been employed in conjunction with streptomycin in eleven cases.

In our cases no correlation has been observed between the amount of the daily dose of streptomycin and sterilization of the urine. Bacteriological arrest occurred in 31 per cent, 29 per cent, and 33 per cent respectively of patients given daily doses of 1 Gm., 2 Gm. and 4 Gm. Urinary concentration of streptomycin of 100 micrograms per cc. is desirable, and in our experience, 1 Gm. of streptomycin daily is the

TABLE III  
STREPTOMYCIN SENSITIVITY OF BACTERIA ISOLATED  
FROM URINARY TRACT INFECTIONS

Type of Bacteria	No. of Cultures Isolated	Sensitivity of Cultures Prior to Treatment		Frequency of Persistence of Bact. Related to Initial Sensitivity	
		Less than 64 micrograms per cc.	Over 64 micrograms per cc.	Less than 64 micrograms per cc.	Over 64 micrograms per cc.
<i>P. aeruginosa</i> . . . .	9	7	2	1	2
<i>S. fecalis</i> . . . . .	12	6	6	0	3
<i>E. coli</i> . . . . .	41	41	0	26	..
<i>A. aerogenes</i> . . . .	16	16	0	8	..
<i>Proteus</i> sp. . . . .	15	15	0	1	..
<i>B. mucosus</i> . . . . .	8	8	0	3	..

tients (89 per cent) which is significantly higher than for the other groups of bacteria. This might indicate that *Proteus* sp. responds at least temporarily more favorably than other bacteria but the alkaline reaction of the urine in infections in which this organism is present may explain the apparently increased susceptibility of *Proteus* sp. infections. Sterilization of the urine may occur quite rapidly following administration

minimum amount which will in most cases insure this concentration.

The strikingly increased antibacterial action of streptomycin *in vitro* at an alkaline pH prompted numerous investigators to suggest alkalinization of the urine in conjunction with streptomycin therapy.<sup>6,9,21,26,27</sup> In sixty-four cases we have treated without the administration of alkali concomitantly with streptomycin bacteriuria ceased in 20 per cent and in eleven cases given alkali during streptomycin therapy bacteriuria disappeared in 73 per cent. (Table iv.)

TABLE IV  
COMBINED USE OF STREPTOMYCIN AND ALKALI IN THE  
TREATMENT OF URINARY TRACT INFECTIONS

Type of Therapy	Total Cases	Bacteriuria after Therapy	
		Present	Absent
Streptomycin without concomitant alkali therapy.....	64	51	13
Streptomycin with concomitant alkali therapy.....	11	3	8

The local use of streptomycin in the urinary tract by irrigation through catheters has not been of value in urinary sterilization in the small number of reported cases.<sup>7,8</sup>

#### FACTORS DETERMINING CURE

It is possible to make a preliminary classification concerning the importance to therapeutic success of the various factors which one must consider in the treatment of urinary tract infections. Data are not yet available concerning the permanency of the cures obtained and it has been previously shown that the usual laboratory tests are of little value in prognosis for patients in whom urinary tract infections have been arrested with sulfonamides.<sup>29</sup>

The largest group of therapeutic failures occurs in patients in whom anatomical

abnormalities of the genitourinary tract are present which prevent the free flow of urine and allow the accumulation of residual urine. Reduction of the number of bacteria in the urine may occur with streptomycin therapy but the bacterial count returns to its former level either during or immediately after termination of treatment. Foreign bodies in the urinary tract such as calculi, indwelling catheters, suprapubic cystostomy or nephrostomy tubes offer a convenient portal of entry for reinfection and predispose to the development of bacteria resistant to streptomycin. Undrained abscesses represent foci which are inaccessible to chemotherapeutic agents and prevent clinical improvement or bacteriological cure. Wounds with granulating surfaces or fistulas communicating with the urinary tract offer such favorable conditions for bacterial growth that sterilization of the urine cannot be accomplished under such conditions.

The development by bacteria of high resistance to streptomycin is to be regarded as the major factor in therapeutic failure. This phenomenon is observed frequently during the treatment of urinary tract infections but also occurs during the treatment of bacteremia and pneumonia. Bacteremia may arise from an organism which has become streptomycin resistant in the urinary tract. We have treated two of these patients in one of whom the etiologic organism was *Pseudomonas aeruginosa* and in the other *Aerobacter aerogenes*. Streptomycin was of no value in controlling the bacteremia in either instance. The method by which streptomycin resistant organisms appear is not completely understood. Resistant bacteria may be derived from sensitive organisms following exposure to streptomycin by a change which occurs in their metabolism or resistant bacteria may be already present in the original culture and grow into predominance following suppression of sensitive organisms. In accordance with the perma-

nence of streptomycin resistance produced by *in vitro* methods is the persistence of resistant organisms in the urinary tract for long periods. Eight patients in whom bacteriuria was present with streptomycin resistant gram-negative bacilli at the termination of streptomycin therapy were re-examined six months after treatment and in all cases resistant bacilli were still present. Other bacteria had appeared in five cases which were sensitive to streptomycin but they had not been present before or during streptomycin therapy and probably represented new invaders. It is of interest, however, that the bacteria recovered at the termination of treatment grew well in the presence of 25,000 to 50,000 units of streptomycin per cc. but those isolated six months later were now sensitive to a concentration of streptomycin of 5,000 units per cc. but resistant to a concentration of 2,500 units per cc.

Mixed infections are more persistent than infections with single organisms. The anatomical lesions associated with mixed infections are frequently more complex and many of the bacteria are resistant to streptomycin. Within the range of bacterial sensitivity to streptomycin which governs the treatment of urinary tract infections variation in sensitivity does not appear to be of importance. Our experience confirms that of others<sup>26</sup> in that bacteria sensitive to a concentration of 2 micrograms per cc. before treatment were as likely to be replaced by highly resistant bacteria of the same type as were organisms with an initial sensitivity of 32 micrograms per cc.

In the presence of bacteria which are within the usual range of sensitivity no additional benefit derives from increasing the dose of streptomycin over that which will insure a urinary concentration of 100 micrograms per cc. In only rare instances was the urine concentration of streptomycin lower than 100 micrograms per cc. when a daily

dose of 1 Gm. was employed providing the fluid intake was limited to 2,500 cc. per day. This is a useful method of conserving material and increasing the concentration of streptomycin in the urine. When fluid intake must be maintained at a higher level the dose of streptomycin should be correspondingly increased. When bacteria of known borderline resistance are present or when *Pseudomonas aeruginosa* or *Streptococcus fecalis* are cultured from the urine a minimum dosage of 2 Gm. is advisable. Increasing the dose in an effort to eradicate resistant bacteria or organisms which are becoming resistant is a practise without rational basis. The use of maximum dosage is indicated at the time treatment is instituted, and when bacteria resistant to streptomycin are known to be present and continuing clinical improvement does not justify prolongation of streptomycin therapy a different chemotherapeutic agent should be selected promptly inasmuch as the response to other agents is not altered by the appearance of streptomycin resistance. The duration of treatment which is necessary to insure the best long term results is not known. In those cases in which sterilization of the urine occurs the urine culture usually becomes negative within seventy-two hours after initiation of therapy.<sup>21,26</sup> In our own experience persistence of bacteriuria after seventy-two hours of treatment signifies the development of streptomycin resistant organisms. Beneficial clinical results may be apparent upon continuation of therapy even though the number of bacteriological cures is not increased.

The concomitant use of alkali and streptomycin to maintain the urine at an alkaline pH at which the activity of streptomycin is considerably enhanced increases the number of bacteriological cures obtained. Sodium bicarbonate, sodium or potassium citrate in doses of 2 Gm. every four hours is usually sufficient to maintain

the urine alkaline. Objections have been made to the use of alkali when *Proteus* sp. is present in the urine since an alkaline medium increases the rate of growth of this organism and encourages precipitation of calcium phosphate.<sup>8</sup> The use of alkali may not be necessary in pure *Proteus* sp. urinary tract infections if the urine pH is carefully followed as the urine is usually alkaline when this organism is present. When infection with a mixed bacterial flora in which *Proteus* sp. is present occurs the urine may become acid following disappearance of *Proteus* sp. and alkali will then be required to maintain the urine at an alkaline pH. Careful observation should be made for the consequences in cardiac patients of fluid retention following a large intake of sodium.

#### SUMMARY

1. After parenteral administration streptomycin appears rapidly in the urine, from which 60 to 80 per cent of the dose administered can be recovered over a period of twenty-four to forty-eight hours after injection. The concentration of streptomycin in the urine is related to the dose administered, volume of urine, and renal function.

2. The bacteria which occur most commonly in urinary tract infections are *Escherichia coli*, *Aerobacter aerogenes*, *Proteus* sp., *Pseudomonas aeruginosa* and *Streptococcus fecalis*. About 75 per cent of the cultures of *E. coli*, *A. aerogenes*, and *Proteus* sp. are sensitive to a concentration of streptomycin of 20 micrograms per cc. or less. Cultures of *P. aeruginosa* and *S. fecalis* frequently occur which are naturally resistant and require a minimum concentration of 100 micrograms per cc. to inhibit their growth.

3. The marked constitutional symptoms and signs accompanying acute pyelonephritis or acute exacerbations of chronic pyelonephritis usually respond dramatically to streptomycin. Mild urinary tract symp-

toms and low grade fever respond irregularly to streptomycin therapy. Definite clinical improvement was observed in 64 per cent of our cases.

4. Limitation of fluid intake to 2,500 cc. daily and a dose of streptomycin of 1 Gm. per day will usually insure a urinary concentration of 100 micrograms per cc. which appears to be adequate for the treatment of urinary tract infections providing other factors are favorable for cure. If *Pseudomonas aeruginosa* or *Streptococcus fecalis* are present a higher urinary concentration is desirable and a daily dose of 2 Gm. should probably be employed.

5. Bacteriuria is diminished temporarily in almost all patients treated with streptomycin. Urinary sterilization occurred in 39 per cent of our cases, with cases in which only a single group of bacteria was present responding more favorably than those in which a mixed bacterial flora was present. Persistence of bacteria after forty-eight hours of treatment usually signifies the development of streptomycin resistance. Exposure to streptomycin does not alter the response of bacteria to other chemotherapeutic agents.

6. The readiness with which bacteria present in the urinary tract develop resistance to streptomycin is the major cause of failure to achieve urinary sterilization. Bacteremia with bacteria resistant to streptomycin may arise from a focus in the urinary tract. Previous treatment with streptomycin may preclude its successful use at a later time because of the persistence of streptomycin-resistant bacteria in the urinary tract.

7. In the presence of anatomical abnormalities presenting indications for urological treatment streptomycin therapy is disappointing. Poor results are to be expected from streptomycin therapy when the following conditions exist in the urinary tract: (1) obstruction which prevents the



free flow of urine and permits accumulation of residual urine, (2) foreign bodies such as calculi or indwelling catheters, (3) wounds with granulating surfaces, and (4) undrained abscesses. Good results are to be anticipated under these conditions only if urological treatment is undertaken prior to or in conjunction with streptomycin therapy.

8. Alkalinization of the urine concomitantly with streptomycin therapy increases significantly the incidence of sterilization of the urine with streptomycin treatment.

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# Streptomycin Therapy in Undulant Fever

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**T**HE first case of "Malta Fever" was recognized in Iowa in 1926. During the following year, forty-three cases were reported to the Iowa Department of Preventable Diseases. Since 1927, the yearly reviews on undulant fever indicate that Iowa has had the largest number of reported cases in the United States. For the first eleven months of 1946, over 500 cases were reported in Iowa and there was only one death. This patient died with congestive heart failure. Blood cultures were positive for *Br. suis* previous to death and the autopsy revealed vegetative endocarditis of the aortic valves. The organisms were isolated in pure culture from the aortic vegetations and the disease was then experimentally reproduced in the guinea pig.

The early cases of undulant fever were diagnosed only by the agglutination test; but later we learned that the agglutination test was not infallible and today we regard a positive agglutination test as only presumptive evidence of active disease. We all know that there are a number of factors that give cross-agglutinations and false positive agglutinins, and thus lead to positive agglutinations for undulant fever in patients that are ill from other diseases. The skin test has never been used as a diagnostic aid in any of my cases. Since 1939, the brucella organism has been isolated from the blood of my undulant fever patients. All patients were seen early in the course of their illness, and this undoubtedly explains in part the large number of positive blood cultures. The diagnosis of undulant fever was not accepted in any of my cases unless the blood culture was positive. I have ob-

served two patients with positive blood cultures in whom the clinical history was suggestive (agglutination positive in a high titre), and yet the patients never lost a day from their work. These patients were observed over a two-year period and they did not have any recurrence of symptoms suggestive of undulant fever. In a few instances a positive blood culture may be obtained in patients not acutely ill. The patient's history, physical findings, exposure, clinical course and complications must be considered along with the laboratory tests before a positive diagnosis of undulant fever can be established.

My first patient was treated in October, 1927, and received enesol (bismuth-mercury preparation) intramuscularly. From 1929 to 1935, many patients were treated with vaccines and brucelline (both in the recommended 0.55 cc. and 1.0 cc. intramuscular injections); and in 1944, intradermal brucelline in 0.1 to 0.22 was used. The heavy brucelline dose was discontinued because of the frequent and pronounced reactions. Very little reaction developed from the intradermal injection. This method was used in four patients but the results were not impressive. Convalescent serum was tried in two patients who were treated in 1939 and in 1940. Both patients had a *Brucella suis* organism in their blood streams. Convalescent serum was obtained from patients with undulant fever who had recently recovered from the disease. Each of the donors had had the *suis* variety of the brucella. The clinical response was satisfactory but it was impossible to secure an adequate serum bank to give this therapeutic agent a con-

vincing test in a large number of patients. Sulfonamide treatments were started in 1939 but the therapeutic results were unsatisfactory. There were many recurrences even though the blood concentration of the drug was maintained at a high level for a period of seven to ten days. In 1944, based upon Tsun Tung's<sup>1</sup> experimental work, patients with undulant fever were treated with a combination of sulfathiazole and penicillin. From 1944 to 1946, twenty-eight of my patients were treated by this combined therapy and twenty-four were improved. There were four failures. Any patient developing a recurrence, even though the relapse was from one to three weeks' duration only, was automatically classified as unsuccessful. The twenty-four patients previously mentioned were successfully treated as far as acute symptoms were concerned; however, the blood culture remained positive at the completion of the treatment and continued positive for one and two months during the convalescent stage. All of my patients had an extended (six to twelve months) period of convalescence. Vitamins, tonics, liver, iron and blood transfusions had no effect in reducing this period in any of these patients.

For a period of nineteen years, then, I have been testing various therapeutic agents in undulant fever, seeking some form of therapy that would clear the blood of organisms and eliminate the profound exhaustive period that followed the patient's recovery from the acute stage. Many patients with undulant fever recover within a relatively short period of simple symptomatic treatment such as complete bed rest until the temperature has been normal for two weeks, wholesome food and vitamins. Eight patients were so treated during 1945 and 1946, and there were six recurrences. This form of therapy had little effect in reducing the patient's exhaustive convalescent period. The mortality rate of

undulant fever has always been regarded as very low, that is, about 3 per cent. However, at the onset of a patient's illness there are no means of forecasting the outcome.

In 1945, when the new antibiotic, streptomycin, was announced, experimental studies indicated that this agent was effective in inhibiting the growth of gram-negative organisms, including brucella. Through the kindness of the Committee on Chemotherapy of the National Research Council, five patients with acute undulant fever were treated with streptomycin between April and September, 1946; and since then a sixth patient has been treated. All of these cases had positive cultures before treatment was started. Blood cultures were obtained daily during the treatment phase and for several days after the completion of streptomycin therapy. Not all of the blood cultures became negative during the treatment phase. In three patients, the blood cultures became negative twenty-four to forty-eight hours after beginning treatment and remained consistently negative during treatment. In three the blood cultures remained intermittently positive during treatment; but in all of them the blood was cultured at weekly intervals after the patient's hospital discharge, for a four-week period, and the blood cultures were negative in each instance. The routine blood examinations were made at the Iowa Lutheran Hospital, Des Moines, Iowa. The blood culture studies were made in Dr. I. H. Bort's laboratory, University of Iowa, Iowa City, Iowa. During the previous year the National Research Council published reports<sup>2,3</sup> of cases of undulant fever treated with streptomycin. They stated that too few cases had been studied to permit any conclusions; however, they expressed the opinion that streptomycin did not strikingly alter the course of the disease in the cases studied. The six patients whom I treated with streptomycin were actually ill with

undulant fever. All of them received daily 500 mg of ascorbic acid intravenously while being treated with streptomycin. Huddleson<sup>4</sup> has indicated that the ascorbic acid level in the blood should be kept as high as possible, since the complement seems to be low during this disease and administration of the vitamin serves to maintain the complement at a high level. There were no chronic cases in this series.

#### CASE REPORTS

**CASE I.** N. C., a colored male, age thirty-four, showed positive agglutination tests (1/1280) for Br. suis infection; tests for typhoid fever and tularemia were negative. Streptomycin treatment was started on the ninety-eighth day of the patient's illness, March 27, 1946. The patient responded immediately to streptomycin. The antibiotic was discontinued on the one hundred third day of illness, April 1st, 1946. This patient received a total of 20 Gm. of streptomycin. There were no reactions to the antibiotic. The blood cultures were positive on the ninety-fifth and ninety-sixth day of the illness, contaminated on the ninety-seventh day, negative on the ninety-eighth and ninety-ninth, positive on the one hundredth and one hundred first day, negative on the one hundred second and positive on the one hundred third to one hundred fifth day inclusive. Unfortunately, no blood cultures were obtained after the patient's discharge from the hospital. The patient returned to his occupation on May 20, 1946. This day would represent the one hundred fifty-sixth day since the onset of his illness.

*Comments.* This was the first patient treated with streptomycin. There were no recurrences of the disease and the clinical response in this patient was satisfactory. In view of our present knowledge, this patient should have been given a larger total dose of streptomycin.

**CASE II.** R. B., a colored male, age twenty-nine, had a blood culture taken on February 19, 1946, which was positive for Br. abortus.

Agglutination tests taken on the same day were positive for brucellosis 1/1280 and negative for typhoid fever and tularemia. This patient was treated symptomatically at his home from February 16 to April 1, 1946. The "non-specific" treatment had no effect upon his symptoms or the course of the disease. The patient was hospitalized on the fifty-first day (April 1, 1946) of his illness. He was then given the combined sulfathiazole-penicillin therapy. The blood sulfonamide level was maintained at 4 Gm. per 100 cc. and 40,000 units of penicillin were given intravenously, every three hours. The patient received this treatment for a seven-day period. Daily blood cultures were negative with one exception. This therapeutic measure was unsuccessful since there was a recurrence of the disease immediately following the patient's discharge from the hospital. On April 24, 1946, the patient re-entered the hospital. Streptomycin was started on the ninety-fourth day of his illness. The blood culture was positive on the ninety-third day and negative from the ninety-fourth to the one hundred third day. Streptomycin was discontinued on the one hundred second day of illness. Blood cultures on the one hundred fourth and one hundred fifth day of illness were positive. The patient's reaction to streptomycin was first apparent on May 27, 1946, by recurrence of the fever, oliguria on May 29th, and a skin rash on May 30th. The blood urea nitrogen, May 29, 1946 was 42.3 mg. per 100 cc. blood. The urine gave a positive reaction for sugar on May 26th, 27th and 30th. Streptomycin was discontinued on the one hundred second day of his illness because of the reactions. The reactions immediately ceased when the antibiotic was discontinued. The total parenteral (intramuscular) dose of streptomycin was 38 Gm. Blood cultures were obtained at weekly intervals after his hospital discharge. All cultures were negative and there were no further recurrences of brucellosis.

*Comments.* Recovery was complete and uncomplicated. A total of twenty-six blood cultures were obtained from this patient during his treatment and convalescent stage.

CASE III. R. T., a white male, fifty-four years of age, had a blood culture taken on April 5, 1946, and *Br. suis* was isolated. On the same day agglutination tests were positive for brucellosis 1/640 and negative for typhoid fever and tularemia. Streptomycin therapy was started on the patient's one hundred forty-fourth day of illness (May 24, 1946). He received a total of 33 Gm. of streptomycin. The antibiotic was discontinued on the seventh treatment day because of reactions. Traces of albumin first appeared in the urine on the third day of treatment and remained present until the drug was discontinued. Hyaline casts and red blood cells were also present in the urine during this four-day period. The test for sugar was positive during the same period that albumin was present in the urine specimen. The blood urea was 25.3 mg. on the sixth treatment day, 25 mg. on the eighth treatment day, 17.4 mg. two days after the streptomycin was discontinued, and 15.0 mg. two days later. A skin eruption first appeared twenty-four hours after streptomycin had been discontinued; however, the rash completely disappeared four days later. Blood cultures were obtained at weekly intervals (for a four-week period) after the patient's hospital discharge. These cultures were negative.

*Comments.* The patient had no recurrence of the disease and there were no remaining after-effects from the streptomycin reactions.

CASE IV. K. W., a colored male, age thirty-six, was treated symptomatically at his home from June 27 to June 29, 1946. His temperature fluctuated between 100° and 104.6°F. during that period. The blood culture was positive for *Br. suis*. Agglutination tests on June 17, 1946, were positive for undulant fever 1/320 and negative for typhoid fever and tularemia. The patient entered the hospital on June 30, 1946, the twenty-second day of his illness. Streptomycin was started on the twenty-fourth day. Reactions were noted early after medication was started. On the first day, the temperature reached 105.4°F. and on the second day there was a chill. The chill might have been

related to the disease and unrelated to the streptomycin. Faint traces of albumin were consistently present in the urine during the treatment phase. Crystals were also noted in the urine specimen during this period. There were no other reactions to the antibiotic. The blood urea nitrogen was always within normal limits. The patient received a total of 51 Gm. of streptomycin between the twenty-fourth and thirty-fourth day of his illness. He was also given 400,000 units of penicillin between the thirty-fourth and thirty-fifth day of his illness. Blood culture reports were as follows: positive on the day that streptomycin treatment was started, negative on the third, fourth, seventh and eighth days, positive on the ninth day, negative on the tenth and eleventh days, positive on the first and second days after streptomycin was discontinued, and negative on the third day following treatment.

*Comments.* The patient's clinical response to streptomycin was considered to be satisfactory in this case. There were no recurrences of the disease. The patient returned to his work on August 20, 1946, which would represent approximately the seventy-third day after the onset of his illness.

CASE V. H. F., a white male, thirty-five years of age, had a blood culture taken which showed the presence of *Br. suis*. Agglutination tests on August 7, 1946, were positive for undulant fever 1/1280 and negative for typhoid fever and tularemia. The patient was first seen on the fifteenth day of his illness. The case was referred to me by Dr. N. Boyd Anderson. The patient's temperature on the fifteenth and seventeenth day of his illness varied from 96.8 to 105.8°F. Sulfathiazole-penicillin was started the eighteenth day of the patient's illness. The patient's blood culture was unknown at that time and I was awaiting permission from the N.R.C. to start streptomycin. This therapy was discontinued on the twenty-first day of the illness and streptomycin treatment was started on the same day. There were no reactions to the antibiotic. The daily blood cultures became negative twenty-four hours after streptomycin was started, and they remained consistently negative.

*Comments.* The patient received a total of 50 Gm. of streptomycin. The clinical results were excellent and there were no recurrences of the disease.

CASE VI. P. B., a white male, age forty-three, had a blood culture taken which showed the presence of Br. suis. Agglutination tests were positive for undulant fever 1/320, negative for typhoid fever and weakly positive for tularemia 1/80. The patient was treated symptomatically for a two-week period. Sulfathiazole-penicillin therapy was started on the twenty-first day of the patient's illness. This form of therapy was discontinued on the twenty-sixth day because of the patient's sensitiveness to sulfathiazole. Streptomycin therapy was started on the twenty-seventh day of the patient's illness. The patient received only 30 Gm. of the antibiotic because of the high cost of this form of therapy. Blood cultures were obtained daily and these became negative twenty-four hours after the treatment was started. There were fifteen blood cultures in all. The cephalin-cholesterol flocculation test was positive before the streptomycin was started and negative at the completion of therapy.

*Comments.* The clinical results were excellent; however, the patient developed a severe generalized eruption over his entire body. An attending dermatologist diagnosed the condition as erythema multiforme bullosum and said that sulfathiazole was probably responsible for the skin complication.

*Streptomycin Dosage.* The total dose of the antibiotic varied for each patient. The daily dosage was 5 Gm., intramuscularly in divided doses of 0.625 Gm., every three hours. Normal saline was used as a diluent. The first patient received 20 Gm. of streptomycin. The second received 38 Gm. but streptomycin was discontinued because of reactions. The third patient received 33 Gm. but the antibiotic was again discontinued because of reactions. The fourth patient received 51 Gm., and the fifth received 50 Gm. The sixth received only 30 Gm.

*Laboratory Data in Each Case.* Daily red

and white blood determinations, blood cultures, and urinalyses were obtained. Every other day blood urea nitrogens and sedimentation rates were done. Hanger's cephalin flocculation test was made in the sixth case at the beginning and at the completion of streptomycin therapy.

*Reactions to Streptomycin.* This new antibiotic should be used with care and patients should be closely observed while receiving this form of therapy. In the present series, no patients developed eighth cranial nerve involvement; however, the routine laboratory tests indicated possible injury to the liver and kidney. The urinary crystals observed were undoubtedly the results of the action of streptomycin upon the kidney, and not streptomycin crystals. This latter is my personal assumption. The reactions promptly disappeared when streptomycin was discontinued. The antibiotic was immediately stopped as soon as a severe reaction appeared.

#### SUMMARY

Our series of six cases is too small to formulate any final conclusions. The experiments were interesting and the results were very encouraging.

In the past, our therapy has been unsatisfactory for two reasons: (1) There were too many recurrences of the original infection, usually from two to five, and (2) extremely prolonged, exhaustive convalescent stage that followed the patient's apparent recovery from the acute phase of his illness; this period varied from four to twelve months. In the six patients treated with streptomycin the following favorable factors were noted: (1) There was an immediate decrease in the elevated temperature. (2) There was an elimination of subjective symptoms (chills, sweats, anorexia, muscle weakness) and earlier return of appetite. In the past I have always regarded the appearance of a ravenous

appetite as a good omen. (3) There were no recurrences or relapses of the infection after the antibiotic was discontinued. (4) There was a marked decrease in the length of the convalescent stage. This was a very significant factor. Convalescence in the streptomycin-treated patients did not extend beyond a sixty-day period.

#### CONCLUSIONS

I believe that streptomycin is an excellent therapeutic agent for the treatment of acute undulant fever. All six patients, as previously explained, responded better to this new form of therapy than to any other

therapeutic measure used in the previous nineteen years. In this series of six cases, five were of the *Brucella suis* and one of the *Brucella abortus* strain. There were no cases of the *Brucella melitensis* variety.

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# Toxicity of Streptomycin\*

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THE toxicity of a chemotherapeutic agent cannot be properly considered apart from the diseases for which it is to be used. Virtually any drug, on occasion, may produce untoward reactions in certain individuals. Evaluation of toxicity, therefore, consists principally in determining the relative dangers of drug and disease. The infections in which streptomycin therapy is of benefit are discussed in the other papers of this symposium. It is against that background of the potential dangers of these individual diseases that the subsequent discussion should be considered.

The problem of the toxicity of streptomycin is complicated by the fact that the preparations which have been in clinical use have varied widely from extremely crude to highly purified substances. Thus, it has not always been possible to establish whether a particular manifestation of toxicity was produced by the antibacterial agent itself or resulted from associated impurities. In a study, which is published elsewhere,<sup>1</sup> an attempt has been made to define the respective rôles of antibacterial agent and impurities by the long continued administration of highly purified streptomycin sulfate to a group of seventeen tuberculous individuals. Subsequent to the study, approximately forty additional patients with tuberculosis have been treated on the same regimen (3.0 Gm. daily) with the same preparation of streptomycin for periods of two to four months. The highly purified streptomycin was prepared from crystalline material\* and is estimated to be at least

95 per cent pure. This experience, together with similar experience with less purified streptomycin, forms the basis of the present discussion.

The untoward reactions which various investigators,<sup>2-9</sup> have observed during the administration of streptomycin are of five general types: (1) the so-called "histamine" reaction; (2) irritation at the site of injection and on topical application; (3) various manifestations of anaphylaxis; (4) evidences of renal irritation occasionally accompanied by impairment of renal function and (5) a neurologic disturbance characterized by vestibular dysfunction and occasionally by deafness.

## HISTAMINE REACTION

The so-called histamine reaction is largely of historic interest, as the substance responsible for its occurrence is no longer present in the preparations of streptomycin which are available for clinical use. The reaction would appear shortly after the intravenous or intramuscular administration of certain lots of streptomycin and was characterized by flushing, headache and an abrupt fall in arterial pressure. The resemblance between the reaction and the phenomena produced by an injection of histamine and the fact that histaminase-treated streptomycin would no longer produce the reaction in animals,<sup>10</sup> constitute the basis for the implication of histamine. The complete

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supplied by the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, chairman, and the remainder was generously donated by Charles Pfizer and Company, Brooklyn, N. Y.

\* A part of the highly purified streptomycin was

\* From the Department of Medicine, Cornell University Medical College and the New York Hospital, New York, N. Y.



absence of this reaction, following the administration of the partially purified streptomycin in general use during 1946 and 1947, indicates that this manifestation of toxicity was produced by a contaminating substance.

#### LOCAL IRRITATION

The intramuscular administration of partially purified streptomycin may, on occasion, give rise to a considerable degree of soreness and induration at the site of injection. There does not seem to be any difference between the sulfate or the hydrochloride salts of streptomycin in the production of this local irritation. Moreover, it would not appear as if the choice of vehicle, distilled water or isotonic saline, plays a significant rôle in the phenomenon. It is virtually certain that pain and soreness at the injection site are caused by adventitious substances which can be removed by a high degree of purification. The highly purified material produced no more local reaction on intramuscular administration at three-hour intervals for 120 days than is observed from the comparable administration of the most highly purified preparations of penicillin in current use.

#### TOPICAL APPLICATION

*Intrathecal Administration.* The intrathecal administration of 0.05 to 0.1 Gm. of partially or highly purified preparations of streptomycin to individuals with or without central nervous system disease is usually well tolerated. Occasionally, particularly when relatively impure material is used, the intrathecal administration of such doses is followed by headache, vomiting and a moderate increase in the number of cells in the cerebrospinal fluid. For this reason it is advisable to use the most purified material available when streptomycin is to be administered by the intrathecal route. It is probable that the *repeated* intrathecal

instillation of streptomycin does produce a slight degree of irritation.

Not infrequently, the patient will complain of pain over the sacrum and posterior thighs during the twelve to twenty-four hours immediately following intrathecal treatment. Usually this symptom disappears after one or two weeks of intrathecal therapy even though the latter is continued.

A sustained pleocytosis in the neighborhood of 200 to 900 cells per cu. mm. is customarily present in the cerebrospinal fluid of individuals with tuberculous meningitis throughout the entire period of intrathecally administered therapy. One or two weeks after the cessation of such therapy, the total cell count usually approaches or attains normal values without appreciable changes in the other components of the fluid. The degree of such irritation must be slight, however, for postmortem examination of four individuals who had received 20 to 100 intrathecal injections of the highly purified streptomycin failed to reveal any evidence suggestive of local irritation in the meninges or brain.

The intrathecal administration of doses larger than 0.1 Gm. (e.g., 0.2 to 0.4 Gm.) may be associated with the appearance of definite signs of toxicity even though highly purified streptomycin is used. Within less than an hour after the treatment, headache, vomiting and nystagmus may appear. During the ensuing twenty-four hours the patient is somnolent and occasionally may be semistuporous. Respirations may be slowed and transient retention of urine in the bladder may occur. During the second twenty-four hours after the intrathecal instillation the evidences of toxicity usually disappear completely. Thus far, no instances of transverse myelitis have been observed. In at least several individuals, however, the repeated intrathecal administration of 0.2 to 0.4 Gm. streptomycin (partially purified) has been associated with

the appearance of delirium which in one instance<sup>11</sup> resembled a Korsakoff's psychosis. In these individuals, the evidences of cerebral involvement slowly disappeared after cessation of streptomycin therapy.

It is possible that accumulation of the drug after repeated administration may be partly responsible for these neurologic reactions. Bio-assay of the cerebrospinal fluid twenty-four to seventy-two hours after an intrathecal injection of 0.2 to 0.4 Gm. of streptomycin usually reveals the presence of an appreciable concentration of the drug.

As streptomycin is administered intrathecally only in the presence of central nervous system infection, it is difficult and frequently impossible to decide whether particular clinical manifestations such as described above represent the results of infection or toxicity. Therefore, when such phenomena are encountered, it is advisable to interrupt the intrathecally administered therapy for a period of several days to a week and to resume therapy only with caution. Moreover, at the present time it would appear that the single dose of 0.1 Gm. for intrathecal administration to an adult should not be exceeded.

*Topical Use Other Than Intrathecal.* An extensive experience has not yet been accumulated on the instillation of streptomycin into body compartments other than the subarachnoid space. From isolated observations, however, it would seem that the introduction of a 1 per cent solution of streptomycin (partially or highly purified) into the pleural or peritoneal cavities is well tolerated.

#### MANIFESTATIONS OF ANAPHYLAXIS

Phenomena which presumably represent manifestations of anaphylaxis are encountered with greater frequency during the administration of streptomycin than during treatment with the sulfonamides or peni-

cillin. Usually, however, it is not necessary to discontinue streptomycin therapy because of these reactions. Three general types of presumed anaphylactic phenomena have been observed: fever, dermatitis and eosinophilia. Although all three types of reaction are frequently present together, each may appear as an isolated phenomenon.

*Fever.* A sustained fever of considerable degree (102° to 104°F.) may occur as an apparent reaction to the administration of partially purified streptomycin. It is by no means certain that sustained fever of this type is a manifestation of anaphylaxis. It is unlikely, however, that such fever reflects the presence of pyrogens in the particular preparation of drug used, for the fever does not usually appear until after five to seven days of therapy. As with drug fevers of other origin the sustained fever of streptomycin therapy is characterized by: (1) the fact that the patient appears much less ill than would be anticipated from the height of the fever; (2) an absence of collateral signs of infection notably leukocytosis and (3) abrupt defervescence after cessation of therapy. It is of interest that fevers of this character have not been observed as yet following the use of highly purified streptomycin.

*Dermatitis with or without Fever.* In a small number (perhaps 5 per cent) of the individuals who receive streptomycin a definite eruption will appear during the second or third weeks of therapy. The rash is identical with the toxic eruptions caused by many other chemotherapeutic agents and may be morbilliform, maculopapular or merely a blotchy erythema. It is usually pruritic and may progress to a superficial scaling dermatitis accompanied by periorbital edema and enlargement of the lymph nodes. The intensity of the constitutional symptoms which may accompany such a reaction varies considerably. In some instances the appearance of the erup-

tion is associated with an influenza-like syndrome with fever, headache, nausea, vomiting, pains in the muscle joints, leukopenia and eosinophilia. Occasionally, at the height of the reaction there is an abrupt fall in arterial pressure. The latter phenomenon is distinct from the histamine reaction described previously and is apparently similar to the nitritoid reaction which is observed during therapy with certain organic arsenicals. In the streptomycin reaction the arterial pressure usually returns to the normal range within a few hours. If streptomycin therapy is discontinued, the constitutional symptoms usually disappear completely within twenty-four hours and the eruption fades during the succeeding week.

In the majority of the patients who develop toxic eruptions, however, the constitutional symptoms are minimal or absent and the principal phenomena are pruritus and eosinophilia. In these individuals the continued administration of the streptomycin is usually associated with a persistence of the itching. Although the latter may be relieved considerably by the use of antihistamine agents such as pyribenzamine or benadryl, the symptom usually persists as long as the patient continues to receive streptomycin.

In addition to these individuals who present frank dermatologic evidence of anaphylaxis, another group, probably equal in size, develop questionable phenomena, which consist of such findings as an ephemeral itching eruption localized to an antecubital fossa or a transient conjunctivitis. It is impossible to be certain that such trivial clinical phenomena are related to the administration of the streptomycin. As with the overt eruptions, however, these trivial and ephemeral rashes usually appear during the first three weeks of therapy and are accompanied by eosinophilia.

*Eosinophilia without Eruption.* In addition

to the individuals who develop eosinophilia in the course of a definite or questionable eruption, a number develop eosinophilia without other evidence of drug sensitization. It is impossible at present, to estimate the precise incidence of this phenomenon but it is apparently high particularly among those individuals who receive streptomycin therapy for several months. Eosinophilia of 5 per cent or more appeared at some time during the four months of therapy in fourteen of the first sixteen patients who received highly purified streptomycin. In nine of these individuals the phenomenon did not appear until the second or third months of therapy.

The eosinophilia varies from an intermittent phenomenon present for one or two weeks at a time, to a constant finding which persists as long as sixty to a hundred days. In general, the eosinophilia ranges between 10 and 15 per cent but not infrequently may be sustained between 25 and 40 per cent for as long as four or five weeks. The percentage of eosinophiles usually falls to within the normal range during the month succeeding the cessation of streptomycin therapy.

In the study of highly purified streptomycin, there was one instance in which sustained eosinophilia was accompanied by an acute synovitis which involved the proximal interphalangeal joints of the hands and feet. As the joint symptoms largely subsided despite continuation of streptomycin therapy the relation of the synovitis to the drug is questionable. Other than this (and save for the eruptions mentioned previously) the eosinophilia observed during the administration of either partially or highly purified streptomycin has not been accompanied by symptoms suggestive of diffuse vascular disease.

*Continuation of Therapy in the Presence of Manifestations of Anaphylaxis.* From available experience with streptomycin it is probable that in most instances no imme-

diately serious situation would be precipitated by continuing streptomycin therapy in the presence of evidences of anaphylaxis. It is not yet established, however, that the sensitivity reactions observed with the use of streptomycin and other chemotherapeutic agents, are transient phenomena completely free from implications concerning the patient's future health. Until the exact significance of drug sensitivity reactions can be established it is advisable to regard them as potentially dangerous and as indications for a complete revaluation of the relative dangers of drug and disease. Thus if the patient is acutely ill or has an infection which continues to constitute a definite threat, it is proper to continue streptomycin therapy despite evidences of anaphylaxis. Conversely, if the infection for which therapy was instituted has largely subsided and relapse is not anticipated, it is advisable to discontinue the antibacterial treatment. There are situations, particularly in the treatment of tuberculosis, in which although the infection carries no immediate threat, it is undesirable to discontinue streptomycin therapy permanently. In such a situation, when manifestations of anaphylaxis appear, it is proper to discontinue therapy and to administer single test doses of streptomycin at weekly intervals. Therapy may be resumed (usually within three to four weeks) when the test doses no longer evoke evidences of drug sensitivity.

#### RENAL FUNCTION

The administration of streptomycin is not infrequently accompanied by cylindruria and occasionally by a minimal degree of albuminuria. On the basis of the experience thus far, it would not appear that these findings represent an important manifestation of toxicity. In a small number of individuals, however, (perhaps .1 to 3 per cent) the administration of streptomycin is associated with a significant reduc-

tion in renal function accompanied by an increase in the concentration of urea nitrogen in the blood. Moreover, the writer has observed one instance of a fatal nephrosis which was apparently produced by the administration of partially purified streptomycin. It should be emphasized, however, that in virtually all instances observed thus far in which significant impairment of renal function has appeared during therapy, overt or probable renal disease had existed before streptomycin treatment was started.

The apparently benign cylindruria is present sporadically during streptomycin therapy and may appear within forty-eight hours of the initiation of treatment. Granular, hyaline and occasionally cellular casts may be excreted. The number of casts varies from a few to as many as fifteen or twenty per low powered field of a centrifuged specimen. The intensity of the cylindruria varies directly with the degree of acidity of the urine. If a neutral or slightly alkaline urine is excreted the cylindruria is minimal or absent. Conversely the cylindruria is accentuated if a highly acid (pH 4.5 to 5.0) urine is elaborated. Cylindruria which is present during the latter part of a course of streptomycin therapy disappears promptly with the cessation of treatment. Although a minimal degree of albuminuria may accompany the cylindruria, hematuria definitely attributable to streptomycin has not been observed.

The nitrogen retention and reduced renal function (urea clearance) which occurs in a small number of treated patients presumably represents a more advanced form of the same process which produces the sporadic cylindruria. The reduction in the urea clearance and the retention of nitrogen usually do not appear until after several weeks of streptomycin therapy. Usually, though not invariably, the renal impairment is accompanied by a moderate degree of albuminuria and cylindruria. The exact

nature of the process is by no means clear. In one instance observed by the writer a reduction in urea clearance to 40 per cent and an increase in blood urea nitrogen to approximately 25 mg. per 100 cc. occurred during the first month of streptomycin therapy and were maintained for approximately three months. Despite the continuation of therapy, however, during the fourth month the values for the urea clearance and blood urea nitrogen slowly returned to normal range. In another individual the urea clearance fell to 20 per cent and the blood urea nitrogen rose to approximately 45 mg. per 100 cc. at the end of a sixty-day course of streptomycin therapy. These values remained essentially unchanged during the four months following the cessation of treatment and during a subsequent ninety-day course of streptomycin therapy.

The instance of fatal nephrosis mentioned previously occurred in a forty-two year old woman who received 4 Gm. of partially purified (1945) streptomycin daily as treatment for a moderately severe typhoid fever. On the fourth day of therapy she developed hemoglobinuria and anuria which terminated fatally approximately twenty-four hours later. At necropsy a severe disseminated necrosis of the convoluted tubules and extensive arteriolosclerosis were present. The tubular necrosis was similar to that seen after the administration of mercuric chloride, uranium nitrate or potassium dichromate. There were no changes in the kidneys which resembled the lesions of typhoid fever. It was considered probable that the observed nephrosis represented a toxic effect of streptomycin on previously damaged kidneys. It should be emphasized that such serious reactions must be rare, for in the treatment of urinary tract infections streptomycin is frequently administered in the presence of renal insufficiency without producing further impairment of renal function.

On the basis of admittedly incomplete information the situation in regard to renal damage from streptomycin may be summarized as follows: (1) Both partially purified and highly purified preparations of the drug give rise to sporadic cylindruria in a large number of instances. This phenomenon is apparently benign, can be largely prevented by the maintenance of an alkaline urine, and is not an indication for the interruption or cessation of streptomycin therapy. (2) In a small number of individuals, chiefly those with pre-existing renal damage, the administration of streptomycin results in a reduction in renal function and an elevation of the blood urea nitrogen. In at least some of these individuals the process is reversible. Until the problem is more clearly defined, however, it is advisable to regard a rising urea nitrogen as a definite indication for either the cessation of therapy or the reduction of dosage to no more than 1 Gm. daily. An additional reason for caution in the presence of renal insufficiency is the possible relationship between the retention of streptomycin and the development of deafness which is discussed below.

#### NEUROLOGIC REACTIONS

The neurologic reactions are undoubtedly the most important toxic reactions to streptomycin and constitute virtually the only serious handicap to the prolonged use of the drug. There are two types of reaction: vestibular dysfunction, which occurs frequently, and impairment of hearing which develops only rarely.

*Vestibular Dysfunction.* The onset of this reaction appears to bear a definite relationship to the size of the daily dose and the duration of treatment. In general, the reaction appears at the end of the fourth week on a 1 or 2 Gm. daily dose; at the end of the third week on a 3 Gm. daily dose and during the second week on larger doses. When a small daily dose (1 or 2 Gm.) is adminis-

tered for only seven to ten days, the reaction does not usually become clinically evident at all. Vestibular dysfunction appears with the same uniformity and apparently the same degree of severity after the use of either partially purified or highly purified streptomycin.

The reaction is characterized by the appearance of headache or a sensation of "heaviness in the head" which disappears within twenty-four hours and is followed by the development of a sensation which resembles vertigo. The symptom differs from vertigo in that a rotary component is lacking. The afflicted individuals experience a sensation of "overshooting the mark" when a sudden movement is made. For example, immediately after completing the movement of rolling over in bed, the patient feels as if he is continuing to roll over and over. On reaching for an object he feels as if his hand is progressing three or four inches past the object although past-pointing is not actually present. Occasionally, the patient will note that there is a momentary delay in focusing the eyes after a sudden change in position.

There is a considerable variation in the degree of vestibular dysfunction noted by different individuals on the same regimen of dosage. In approximately one-third of the patients (who receive a streptomycin for one month or more) the reaction is negligible and discovered only by careful questioning. In the remainder, the disorder is moderately severe or severe. In such instances, at the peak of the reaction, the patients are unable to walk or to sit up in bed unassisted and may be acutely uncomfortable even while lying flat. Nausea is likely to be produced by change in position and may be accompanied by vomiting. The symptoms usually persist in acute form for seven to ten days and then subside to the point where only an unusual stimulus such as a sudden shaking of the head would produce the symptoms

momentarily. Some individuals, however, although symptom-free while sitting erect in bed, may have difficulty when an ambulatory regimen is resumed. In the majority of instances the symptoms of minimal vestibular dysfunction persist for approximately sixty to ninety days and then disappear except when the individual attempts to walk in complete darkness. A minority of those afflicted (precise number not yet established) have some difficulty in walking even in the daylight for as long as six or eight months after the acute reaction. Usually, however, as long as the individual can orient himself visually, he can walk without obvious ataxia. It should be noted that such individuals do not have to watch their feet while walking but unconsciously maintain their balance by orienting themselves to any fixed objects.

Nystagmus appears in association with the vestibular dysfunction in surprisingly few instances. With the use of quantitative technics for caloric stimulation it is usually possible to demonstrate hypofunction of the vestibular apparatus which persists for many months after the acute reaction.

The mechanism by which the vestibular dysfunction is produced is not known and presumably the site of the lesion may be either in the labyrinth or in the brain. There is evidence which suggests that at least part of the dysfunction is in the nature of an intoxication which is reversible up to a certain point, but which results in more persistent damage if the administration of streptomycin is continued. For this reason it is advisable to discontinue streptomycin at the first sign of dysfunction, or preferably to stop therapy before the time at which the reaction customarily appears.

If the nature of the infection which is being treated is such that the cessation of therapy is inadvisable, symptomatic recovery, as described above, will occur despite the continued administration of streptomycin.

cin. It should be realized, however, that such immediate recovery apparently represents the activation of compensatory mechanisms and does not reflect a return of vestibular function. As would be anticipated, the degree of compensation varies among individuals and may be appreciably less complete in elderly individuals. It is not known whether any degree of vestibular (i.e., not merely symptomatic) recovery is to be expected in those individuals whose dysfunction has persisted for many months after the cessation of therapy. From a few isolated observations<sup>12</sup> there is reason to hope that in some instances at least, true functional recovery may be possible.

*Deafness.* In the Cornell-New York Hospital series, bilateral nerve deafness ranging between 50 and 100 per cent in extent, occurred in seven of the first one hundred patients who received streptomycin. The reaction occurred following the use of the highly purified streptomycin as well as after administration of the less pure material. The significance of this reaction, in terms of the toxicity to be expected from streptomycin, is much less alarming, however, than is suggested by this relatively high incidence. Five of the seven individuals had tuberculous meningitis and had received prolonged streptomycin therapy by the intrathecal route. The two patients who became deaf in the absence of meningitis (or intrathecal therapy) had marked renal insufficiency which resulted in the persistence of unusually high concentrations of streptomycin in the blood. Moreover, aside from these two types of cases, deafness was observed in the Mayo Clinic series only in patients who received unusually large doses of streptomycin (5 to 10 Gm. daily). Thus in the combined Mayo Clinic and Cornell-New York Hospital series, deafness has appeared in only three types of cases: (1) individuals who have received unusually high daily doses; (2) individuals who have

received 1 to 4 Gm. daily in the presence of marked renal insufficiency; (3) individuals (with tuberculous meningitis) who have received streptomycin intrathecally.

The limitation of the reaction to these three types of cases strongly suggests that the development of deafness during streptomycin therapy is largely a result of overdosage. To be sure, if an excessively large dose of a drug can produce a reaction such as deafness in some patients, it is to be anticipated that some unusually susceptible individual will develop the same reaction on what is ordinarily considered to be a small dose of the drug. On the basis of present experience, however, it would seem that deafness as a result of therapy represents only a small hazard to patients with normal renal function who receive only 1 to 3 Gm. of streptomycin each day by the intramuscular route. In some instances, the deafness which may appear in the course of meningitis is presumably caused by the infection and not by intrathecally administered streptomycin. It is reasonable to assume, however, that the introduction of such relatively large quantities of streptomycin directly into the subarachnoid space contributes to the development of deafness.

Because of the possibility of deafness, it is advisable to obtain an audiometric examination on all patients who are to receive streptomycin. The examination should be repeated routinely at fortnightly or monthly intervals and even more frequently in the presence of meningitis or impaired renal function. If any reduction in hearing develops, streptomycin should be discontinued immediately save in the presence of an infection which is customarily fatal in the absence of antibacterial therapy. Brown and Hinshaw<sup>9</sup> have observed that the presence of a constant, roaring, low-pitched tinnitus frequently precedes the appearance of deafness. High-pitched, intermittently present tinnitus, is so ubiquitous a symptom with or

without streptomycin therapy, that its value as a warning of incipient deafness is questionable.

From the preliminary studies of Stevenson, Alvord and Correll,<sup>13</sup> it appears that the site of toxic action which results in deafness is in the brain. These investigators noted liquefaction necrosis of the ventral cochlear nucleus in the tissues of three patients of the New York Hospital series who had developed deafness during therapy with highly purified streptomycin. Similar lesions were also found in the brain of one dog who had received intensive treatment with partially purified streptomycin. It is of interest that in the brain of one of the patients the same type of lesion was present in the vestibular nuclei, which suggests that the site of the vestibular toxicity is also centrally located.

There has not yet been sufficient experience to permit an estimation of the degree of recovery of hearing which is to be anticipated in those patients who have suffered a reduction in hearing during therapy. About all that can be said is that in some instances considerable improvement (30 to 50 per cent) has occurred. Presumably, however, in many instances the loss of hearing is permanent.

Other than the reactions involving vestibular or cochlear function, no effects of streptomycin upon the nervous system have been noted.

#### MISCELLANEOUS MANIFESTATIONS OF TOXICITY

Leukopenia (1,500 to 3,000 cells per cu. mm.) occasionally accompanied by a relative granulocytopenia has been observed during the course of streptomycin therapy. The few cases in the Cornell-New York Hospital series were all in patients with acute hematogenous tuberculosis, a condition in which involvement of the bone marrow is not uncommon. Despite the con-

tinuation of streptomycin therapy, the total leukocyte counts eventually rose to within the normal range. In the event that granulocytopenia should be observed in the absence of miliary tuberculosis it would be advisable to consider it as a manifestation of toxicity and an indication for the immediate cessation of streptomycin therapy.

One instance of thrombocytopenia has been observed in a patient with acute brucellosis who was receiving 6 Gm. of streptomycin daily.<sup>14</sup> Recovery was prompt and complete after the discontinuance of therapy.

No evidence has been obtained which would indicate that the administration of streptomycin results in anemia or in damage to the liver.

#### SUMMARY

The administration of streptomycin by the intramuscular route in a daily dose between 1 and 3 Gm. is well tolerated for a one or two-week period by most individuals. With the single exception of vestibular dysfunction the same dose regimens are well tolerated by most individuals for periods as long as four months. Although daily doses larger than 3 Gm. are apparently well tolerated by some individuals for short periods of time, it is probable that 3 Gm. represents the upper limit of the safe daily dose.

The histamine reaction, irritation at the site of injection and possibly the sustained febrile reactions are not caused by streptomycin but by impurities which are removable with refinements in the process of manufacture. All of the other manifestations of toxicity which have been observed after the use of impure streptomycin have also occurred during the administration of highly purified preparations of the drug.

The toxicity of streptomycin is sufficiently low to justify the use of the drug in serious or potentially serious infections. Con-



versely, the incidence of toxicity, notably vestibular dysfunction, is sufficiently high after several or more weeks of therapy, that the drug should not be used for infections with a generally favorable prognosis such as minimal pulmonary tuberculosis or chronic brucellosis.

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## Acute Coronary Artery Diseases

### *History, Incidence, Differential Diagnosis and Occupational Significance*

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**A**CUTE coronary artery disease did not suddenly appear in the twentieth century; it has existed for hundreds, probably thousands of years. There is evidence that it occurred among the early Egyptians. Ruffer<sup>1</sup> writing "On arterial Lesions Found in Egyptian Mummies (1580 B.C.—525 A.D.)" stated that the Egyptians of 3,000 years ago not only suffered from calcification of the arteries, but that the arteriosclerosis at that time was of the same nature as this disease today, that is, calcification following atheroma.

From his investigations, Ruffer concluded that the stress and strain of modern life, exertion, meat diet, tobacco, alcohol and syphilis are not contributory factors in the production of coronary disease. Previously reported observations of my colleagues and myself<sup>2</sup> support this conclusion. In a series of cases of acute coronary occlusion we could not find any precipitating factors, and believe that this disease is solely a sequel to arteriosclerosis of the coronary arteries.

Brim<sup>3</sup> has interpreted certain passages in the King James translation of the Bible from the standpoint of modern medicine and he believes that some of the accounts of sudden death represent acute coronary occlusion. For example, "In the case of Sichon the king of Cheschbon, the Lord hardened his heart, and closed his heart, and he was therefore delivered unto your power." (Deut. 2:30).

Reisman and Harris<sup>4</sup> point out an illustration of "instantaneous painless coronary death" to be found in Homer's *Odyssey*. "Phoebus Apollo shed down his gentle darts upon Prontis, son of Onetor, Manetaus' navigator, and he dropped dead with the steering oar of the moving ship within his hands."

Hoffman<sup>5</sup> writes that Hippocrates of Cos in his "Prognostics" said that "Cardiodynia which occurs more frequently in senility foretells sudden death."

Many a physician before Heberden<sup>6</sup> must have observed episodes of angina pectoris. Seneca<sup>7</sup> recorded his own suffering from this disease, as did the Earl of Clarendon.<sup>8</sup> But it was Heberden who, as the result of observation of a hundred patients in his daily practice, established the syndrome of angina pectoris as a clinical entity. His account written in 1768 reads like a recent textbook of the disease.

In spite of his knowledge of angina pectoris, Heberden did not realize that there was any relationship between this syndrome and disease of the coronary arteries. Credit must be given to Edward Jenner<sup>9</sup> and Caleb Parry<sup>9</sup> for the establishment of this connection. These authors did not publish their ideas until the death of their mutual friend John Hunter, because the latter was a victim of angina pectoris.

*Experimental Investigations.* While knowledge of the clinical manifestations of disease

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of the coronary arteries was accumulating, the experimental work which would eventually lead to the conception of the function of these vessels of the heart lagged behind. Chirac,<sup>10</sup> in 1698, reported that ligature of the coronary arteries in the dog produced a standstill of the heart. This observation is merely of historical interest for it bore no fruit. In 1698 there was no appreciation of the clinical importance of the coronary vessels.

In 1842, Hall<sup>11</sup> contended that ossification of the coronary arteries could cause a fatal outcome, and that abrupt obstruction would produce sudden death. To test this theory, Ericksen<sup>12</sup> conducted some experiments on animals. He concluded that arrest of the coronary circulation produced cessation of the heart's action and that an increase in the quantity of blood sent into or retained in the muscular fibers of the heart caused a corresponding increase in the activity of that organ.

Burns<sup>13</sup> compared the action of the heart supplied by calcified arteries with the action of a limb around which a ligature has been applied. "Exercise, passion, and ardent spirits" he considered a danger to a heart so affected.

In recent years, Keefer and Resnick<sup>14</sup> showed that anginal pain was due to anoxemia. Sir Thomas Lewis<sup>15</sup> was of the opinion that this pain was caused by accumulation of chemical poisons.

In 1935, Tennant and Wiggers<sup>16</sup> observed that immediately following occlusion of branches of the coronary arteries in dogs, the ischemic areas ceased to contract. Then the involved area bulged passively while the remainder of the ventricle contracted normally. This reversal of pulsation or "paradoxical" pulsation was observed fluoroscopically in man by Master and his co-workers.<sup>17</sup>

*Acute Coronary Artery Occlusion.* Coronary disease has been shown to have existed in

ancient times and the association between angina pectoris and sclerosis of the coronary arteries was first made in the eighteenth century. The actual appreciation of acute coronary occlusion as a definite disease, that is, as a special form of coronary sclerosis, is of relatively recent development.

In 1878, Hammer<sup>20</sup> described an instance of coronary thrombosis in an article entitled, "A Case of Thrombotic Occlusion of One of the Coronary Arteries of the Heart." He diagnosed the condition before death in a patient who suffered sudden collapse accompanied by a ventricular rate varying from but 8 to 40 beats a minute. The heart sounds were faint. At autopsy a thrombus was found in the right sinus of Valsalva, closing the ostium of the coronary artery. This case is probably the first instance in which complete heart block in coronary occlusion is described.

In 1880, Winsor,<sup>18</sup> a physician who practised in Winchester, Massachusetts, presented a paper entitled, "Angina Pectoris with Rupture of the Heart." This author clearly recognized the relation of coronary thrombosis to preceding disease of the coronary vessels and realized that the myocardium became "degenerated" with rupture of the involved wall.

Huber<sup>19</sup> (1882) related necrotic and fibrotic lesions in the myocardium to atheromatosis of the coronary artery.

In "Some Notes on the Coronary Arteries" published in 1896, George Dock<sup>21</sup> reported a case in which antemortem diagnosis of coronary thrombosis was made in a man sixty-four years old.

In 1910, two Russians, Obratzow and Straschesko<sup>22</sup> discussed the clinical aspects, diagnosis and pathological anatomy of occlusion of the coronary arteries, and the consequent infarction and myomalacia of the heart.

Hochhaus,<sup>23</sup> in 1911, reported four instances of acute coronary artery occlusion,

two of which were correctly diagnosed before death with experience gained from the other two.

Notwithstanding these early reports, knowledge of acute coronary artery occlusion did not become at all general until Herrick,<sup>24,25</sup> presented a complete clinical and pathological picture of this disease in his two brilliant reports published in 1912 and 1918. He showed that the coronaries are not strictly end-arteries, but that they develop functioning anatomic anastomoses; he discussed the symptoms of coronary thrombosis, the pericardial friction rub; he pointed out that occlusion of a large branch of a coronary artery or even of a main trunk need not necessarily cause sudden death.

In 1929, Levine<sup>26</sup> published his monograph, "Coronary Thrombosis." In this carefully detailed study was assembled all the available knowledge concerning coronary thrombosis, clinical electrocardiographic, pathological and therapeutic.

Fred Smith<sup>27,28</sup> and H. E. B. Pardee<sup>29</sup> first correlated the electrocardiographic observations with clinical evidence of acute coronary occlusion.

"*Acute Coronary Insufficiency*" (*without Acute Occlusion.*) Acute coronary occlusion is now a well recognized disease. Indeed, its features are so well marked that they have tended to obscure recognition of another, equally important product of coronary artery sclerosis, that is, "acute coronary insufficiency" (without acute occlusion) or myocardial ischemia or necrosis (infarction) without acute coronary occlusion. This condition, has been recognized in the German literature,<sup>30-34</sup> but only recently has its importance been appreciated in this country.<sup>35-39</sup> My colleagues and I have presented evidence to show that acute coronary insufficiency without acute occlusion is a disease entity with specific etiologic features, and characteristic pathologic and electrocardiographic pat-

terns.<sup>38-40</sup> This condition is not however, sufficiently widely recognized, and the importance of differentiating acute coronary insufficiency without acute occlusion from acute coronary occlusion cannot be over emphasized.

Although acute coronary insufficiency (without acute occlusion) was not recognized as a disease entity until less than twenty years ago, the writings of some of the early physicians show a certain perception into the nature of this phase of arterial sclerosis. Parry,<sup>9</sup> for instance, in speaking of ossification of the coronary arteries noted that such a heart "may be fit" during a state of mental tranquillity, yet when any unusual exertion is required, its power may fail.

#### MAGNITUDE OF CORONARY DISEASE

It has become clear that heart disease has been since 1912 the chief cause of death in this country.<sup>41-44</sup> In 1942, almost 400,000 persons died of cardiac disease alone, about 28.5 per cent of all deaths.<sup>42</sup> It is probable that at least 4,000,000 persons in the United States are afflicted with heart disease. One survey gives an estimate of double this figure, placing the total at 8,000,000.<sup>45</sup>

TABLE I  
CAUSE OF DEATH FOUND IN POSTMORTEM EXAMINATION OF  
489 CASES OF CARDIAC DISEASES—THE MOUNT SINAI  
HOSPITAL, N. Y. 1932-1938

Period	No. of Cases	Acute Coronary Diseases Per Cent	Rheumatic Heart Disease Per Cent	Congenital, Luetic, Misc. Per Cent
1932-36	310	45.0	26.0	29.0
1937-38	179	54.0	28.0	18.0

Various writers have reported that acute coronary diseases comprise 25 to 40 per cent of all heart diseases.<sup>46</sup> In an investigation of different types of cardiac diseases carried on between 1932 and 1938, careful postmortem

TABLE II\*

	Acute Coronary Insufficiency	Acute Coronary Occlusion
Synonyms.....	Acute coronary insufficiency without acute occlusion Myocardial necrosis or infarction without acute coronary occlusion Subendocardial necrosis or infarction	Acute coronary insufficiency with acute occlusion Acute coronary thrombosis Myocardial infarction due to coronary artery occlusion
Mechanism.....	Decreased supply of oxygen or blood to the myocardium or disproportion between the supply and the demands of the latter Transient, slight, to prolonged and severe anoxia or ischemia Reflex vasoconstriction frequent	Complete occlusion of a coronary vessel  Complete ischemia  No reflex mechanism
Pathology.....	Coronary artery involvement variable—vessels normal to severely diseased; usually sclerotic No acute muscle changes in simple episode of angina pectoris In severe form diffuse, disseminated focal areas of necrosis in subendocardium and papillary muscles No, or little involvement of the pericardium or endocardium and hence no pericarditis or mural thrombosis with embolization	Coronary arteries invariably diseased Infarction—massive, confluent extending from endocardium to pericardium Pericarditis and frequent mural thrombosis with embolization
Predisposing.....	Arteriosclerotic, hypertensive, valvular and luetic heart disease	Arteriosclerotic and hypertensive heart disease
Exciting.....	Effort, emotion, extremes of heat and cold, food, tobacco plus liquor, valvular heart disease, anesthesia, operation, shock, heart failure, tachycardia, auricular flutter or fibrillation, fluctuations in blood pressure, hypoglycemia, adrenalin, anoxemia, carbon monoxide poisoning, hemorrhage, anemia, pulmonary infarction and embolism, status asthmaticus, visceral reflexes, sexual intercourse, straining at stool, infection, trauma, hyper- and hypothyroidism	None Possibly operation, shock or drop in blood pressure?
Laboratory Findings.....	None in simple attack of angina pectoris If myocardial necrosis present, then fever, leukocytosis, rapid sedimentation rate—but usually not very marked	Fever, leukocytosis, rapid sedimentation rate
Fever.....	None or slight	Constant, 100° to 103°f. usually
Pain.....	Slight to severe Usually relieved by nitroglycerin	Usually severe Not relieved by nitroglycerin, in fact condition aggravated
Gastrointestinal.....	Nausea and vomiting not present in simple attack of angina pectoris	Nausea and vomiting common
Cardiovascular:		
Shock.....	Usually absent	Common
Heart Sounds.....	Usually no change	Poor, tic-tac, embryocarditic, gallop
Pericardial Rub.....	Absent	Present
Blood Pressure.....	Usually no change; may rise during pain	Definite fall
Tachycardia and arrhythmias	Usually absent except as a precipitating agent	Common after the onset
Heart Failure.....	Variable	Common; lungs often congested

TABLE II\* (Continued)

	Acute Coronary Insufficiency	Acute Coronary Occlusion
Electrocardiogram . . . . .	RS-T depressions T wave inversions	RS-T elevations into T wave inversions Large Q-waves Reciprocal relationship between leads I and III
Treatment . . . . .	Preventive and curative Avoid cause and treat exciting factor; transfusion for hemorrhage, digitalis for heart failure, etc.	No specific treatment except for complications
Duration of Illness . . . . .	Seconds, minutes, hours and days	Weeks, months and years
Condition after Attack . . . . .	Good in angina pectoris; variable otherwise	Poor
Degree of Recovery . . . . .	Complete for single attack of angina pectoris; variable otherwise	Prolonged illness and earmarks of attack for years
Prognosis . . . . .	Variable; depends on precipitating factor	Fatal outcome not uncommon; signs and symptoms usually permanent
Compensation . . . . .	Compensable	Not directly compensable

\* Slightly modified from *New York Medicine* 2: 9, 1946.

examination of the hearts revealed that the proportion of deaths due to acute coronary artery diseases was 49.5 per cent, and for the year 1938 was actually 54 per cent. (Table I.) It is obvious, then, that coronary diseases are by far the most important of all heart diseases.

With the lengthening span of life, and an increasing older population, the number of victims of coronary disease will continue to increase. According to the National Resources Planning Board<sup>47</sup> there were in this country in 1900, 8,500,000 persons between the ages of fifty and seventy-four years; in 1940, 24,000,000, and in 1980 there will be 42,000,000. Since two thirds of the episodes of acute coronary diseases occur in this older age group it is apparent that the number of cases will be even greater than it is today.

#### DIFFERENTIATION OF ACUTE CORONARY DISEASES

There are two main divisions of the acute coronary diseases: (1) acute coronary occlusion, and (2) "acute coronary insufficiency" (without acute occlusion.)

*Acute coronary occlusion*, (Table II) is the term used to indicate sudden complete

closure of the coronary artery, a sequel of progressive arteriosclerosis. The attack occurs fortuitously, at any time, anywhere, and is not related to effort and excitement. In fact, it takes place most frequently during sleep and rest, simply because the major part of the day is spent in these states. The symptoms and signs of crushing substernal pain (not relieved by nitroglycerine), nausea, vomiting, shock, fall in blood pressure, change in heart sounds, gallop rhythm, fever, leukocytosis and increased sedimentation rate, are well known. The illness is prolonged and usually results in permanent changes in the heart. At autopsy, the lumen of the coronary artery will be found completely closed by a thrombus formed directly on an arteriosclerotic plaque, or originating from an intimal hemorrhage breaking through the endothelial lining of the plaque. Occasionally a hematoma within an intimal plaque causes complete obstruction of the lumen without thrombosis. The infarct is large, usually extending from the endocardium to the pericardium. The resulting pericarditis may give rise to a friction rub. Involvement of the endocardium frequently results in mural thrombus forma-

tion and peripheral embolization. The electrocardiogram is specific. Elevations of the RS-T segments progress steadily to inverted T waves. Large Q waves and a reciprocal relationship between Leads I and III are present. The RS-T elevations are associated with the epicardial and subepicardial involvement, the Q waves with the massive through-and-through injury to the ventricular wall, possibly septal damage.

In *acute coronary insufficiency (without acute occlusion)* (Table II) there are gradations of severity of the heart attacks. The simple short episode of angina pectoris, in which the chest pain is momentary, is brought on by exertion, excitement, ingestion of food, cold, and the like, and is relieved by nitroglycerine and rest. Gastrointestinal manifestations, fever, leukocytosis and increased sedimentation rate are not present. When the pain has disappeared, the patient's condition is good. The blood pressure does not fall; in fact, it may rise. Acute alterations in the myocardium do not occur. An electrocardiogram taken during an attack may show transient RS-T depressions and T wave inversions, or it may be normal.

In a more severe type of acute coronary insufficiency (without acute occlusion), the anoxia of the heart muscle is prolonged so that serious injury to the latter may take place. A synonymous term for this type of attack is acute myocardial necrosis without acute occlusion. The chest pain may be severe and moderately prolonged. The episode is often related to exertion, excitement and emotion. It may occur after sexual intercourse, straining at stool or following gastroenteritis. It may be induced by extremes of heat and cold, tachycardia, auricular fibrillation or auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of many types, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism and hypothyroidism. It is a consequence of pulmonary infarction and embolization, of

infection and trauma; it occurs reflexly from abnormal or diseased abdominal viscera. The symptoms and signs are those to be expected in a disease that is more serious than the simple syndrome of angina pectoris, but frequently they are not so grave as similar manifestations of acute coronary artery occlusion. Chest pain, shock, change in heart sounds, fall in blood pressure, fever, leukocytosis and increased sedimentation rate, if present, are usually not so marked as in acute coronary occlusion. In a severe episode, the heart muscle may contain many focal, or even diffuse, areas of subendocardial necrosis. These areas are often observed in the papillary muscles, but the endocardium and the pericardium are not involved. For this reason, thrombus formation on the heart wall with subsequent embolization is not encountered and pericardial rub is not heard. The electrocardiogram discloses depressions of the RS-T segments and T wave inversions in one or more leads. The localization of the myocardial necrosis to the subendocardium may be explained by the assumption that this region of the myocardium receives the poorest blood supply. Small branches from the coronary arteries turn at right angles into the cardiac muscles and beneath the endocardium. Hence, this area is farthest from the source of nourishment and suffers most when the coronary flow is diminished. The endocardium itself receives blood directly from the ventricular cavity.

The differences in the electrocardiograms in coronary insufficiency and coronary occlusion can be explained by the dissimilar pathologic changes. It has been suggested<sup>56, 65, 66</sup> that the elevation of the RS-T segment in coronary occlusion is associated with the pericardial involvement common in this condition. In coronary insufficiency, the areas of necrosis are focal and scattered and chiefly subendocardial; the pericardium is spared. Therefore, depression of the RS-T interval replaces elevation of this segment.

Recently Boyd and Scherf<sup>58</sup> showed that injury to the epicardium at the apex of the heart produces a high take-off of the RS-T segment, whereas injury to the endocardium produces depression of this segment with slight inversion of the T waves.

The prognosis of acute coronary insufficiency without acute occlusion, even when myocardial necrosis is present, is usually better than that of acute coronary occlusion with infarction.

Treatment of these two types of acute coronary diseases differs. A rational existence, mentally and physically, a change in climate, avoidance or elimination of known precipitating causes such as unusual or severe effort, trauma, overexcitement, extremes of heat and cold, overeating, excessive smoking together with drinking, will prevent acute coronary insufficiency without acute occlusion. During operation or anesthesia an adequate supply of oxygen must be administered in order to avoid cyanosis. Adequate treatment, or better, prevention of shock is indicated. Administration of digitalis and the mercurial diuretics in heart failure, digitalis and quinidine for tachycardia, auricular fibrillation and flutter, blood transfusions for hemorrhage or anemia, avoidance of reflexes from the abdominal viscera, prevention or cure of infection perhaps by means of the sulfonamide drugs, penicillin and streptomycin, are all measures of value in preventing acute damage to the heart muscle. In acute coronary occlusion, on the contrary, avoidance of these predisposing factors will not prevent the onset of acute coronary occlusion. The best treatment for this is passive; active or drastic measures should not be employed unless complications make it necessary to intervene.

#### CONFUSION OF TERMS AND THOUGHT

It would be well to point out the existing confusion in the terminology employed in coronary artery diseases.<sup>48</sup> A number of ex-

pressions in use, including angina pectoris, coronary occlusion and coronary thrombosis, coronary insufficiency, coronary failure and myocardial infarction, are often applied loosely and given various connotations.

The distinction between acute coronary insufficiency and acute occlusion is confused by careless use of terms. The term, acute coronary occlusion should be applied only to sudden complete obstruction of a vessel. The clinical syndrome and the electrocardiographic findings are characteristic and the diagnosis is readily made. The adjective "acute" should be employed in order to distinguish the sudden catastrophic episode from chronic progressive arteriosclerosis of a coronary artery resulting in partial or practically complete obstruction of the lumen. Blumgart and Schlesinger,<sup>49</sup> in their otherwise excellent investigation, used the term coronary occlusion to indicate arteriosclerotic narrowing whether or not there was acute complete occlusion.

The expression "acute coronary insufficiency" should be employed in the restricted sense which we have used. It should not be employed to include all of the acute coronary diseases as is so frequently done. Of course, the qualifying phrases "with acute occlusion" or "without acute occlusion" would be descriptive and most accurate, but experience has shown that few have adopted them.

The term "myocardial infarction" is sometimes used without qualification, an unfortunate circumstance, since the meaning of this term is too broad to permit of its being an exact diagnosis. When "myocardial infarction" is employed, its meaning should be delimited by adding either "with acute coronary occlusion" or "without acute coronary occlusion."

In addition to recognition of the clinical variations in the several coronary artery diseases and to properly defined terminology, correct diagnosis will be further assured if electrocardiographic changes are properly



interpreted. The presence of RS-T elevations alone are characteristic of pericarditis<sup>50</sup> but not of acute coronary occlusion.<sup>51</sup> RS-T depressions which appear alone are typical of involvement of the inner or subendocardial region of the heart<sup>36, 52, 53</sup> and should not be interpreted (which frequently happens<sup>54, 56</sup>) as indicative of acute coronary occlusion. Many investigators have shown that damage to the inner surface of the heart results in RS-T depressions, whereas epicardial injury is associated with RS-T elevations.<sup>50</sup>

The clinical and electrocardiographic characteristics of the various acute coronary diseases have now been so extensively verified by postmortem examination that with proper appreciation of these characteristics, diagnosis in any given case can be made with assurance. The classical clinical signs and electrocardiographic pattern of acute coronary occlusion will be corroborated at autopsy in 95 per cent of the cases.<sup>40, 57</sup>

#### INCIDENCE OF ACUTE CORONARY OCCLUSION

The incidence of acute coronary occlusion is not readily obtainable. The census includes acute coronary occlusion under diseases of the coronary arteries and angina pectoris. An estimation of the actual number of deaths from acute coronary occlusion was made by sampling New York State death certificates and applying the figures thus derived to the rest of the country. It was computed<sup>58, 59</sup> that at least 25 per cent of deaths reported under "diseases of the myocardium," 60 per cent of those ascribed to "coronary disease" and 80 per cent of those listed as "angina pectoris" were, in fact, instances of acute coronary occlusion. On the basis of these percentages, it was calculated that there were 120,000 deaths from acute coronary occlusion in this country in 1942. If the mortality rate for this disease is accepted as 15 per cent, there are about

800,000 attacks of acute coronary occlusion yearly.

Using the United States census figures<sup>58</sup> for the number of men and women in this country over forty years of age, and a coronary disease incidence ratio of 3 men to 1 woman, we may conclude that approximately 1 man in 40 and 1 woman in 115 experiences an attack of acute coronary occlusion yearly. These figures will, of course, vary if other mortality rates are adopted for the computation. There is evidence<sup>59</sup> that the number of instances of acute coronary occlusion may be as high as 1,000,000; if this figure is accepted, 1 man in 30 and 1 woman in 90, forty years of age and over, annually sustain acute complete obstruction of a coronary artery.

#### INCIDENCE OF "ACUTE CORONARY INSUFFICIENCY"

It is my opinion that the incidence of acute coronary insufficiency (without acute occlusion) is of the same magnitude and significance as is that of acute coronary occlusion. Although further and extensive tabulation of the comparative incidence of these two types of coronary artery disease is needed, certain figures to be found in recent reports are significant. Kroetz<sup>60</sup> believes that acute coronary occlusion and acute coronary insufficiency without acute occlusion occur with equal frequency. He found acute occlusion in 55 per cent of his cases and acute coronary insufficiency without occlusion in 45 per cent.

Levy and Bruenn<sup>61</sup> in a review of the postmortem examinations of 376 cases in which death was due to coronary sclerosis, found only thirty-nine instances of coronary thrombosis. This is, of course, an unusually low percentage, and the authors themselves point out that a close examination of the coronary arteries would undoubtedly have brought to light many more instances of acute occlusion.

French and Dock<sup>62</sup> describe eighty deaths from acute coronary artery disease which occurred among young soldiers. Only twenty-nine or 36 per cent of the deaths were cases of acute coronary occlusion, and I believe the majority of these actually represented acute coronary insufficiency without acute occlusion.

A review of the autopsies at the Mount Sinai Hospital, New York, for the five years 1941–1945 inclusive, reveals that about 70 per cent of deaths from acute coronary disease were due to acute occlusion; in the remaining 30 per cent acute occlusion did not occur. These figures are merely approximate, and in the near future we hope to obtain accurate ratios.

Although the foregoing statistics obviously do not furnish adequate evidence on which to base conclusions, they do indicate that deaths from acute coronary insufficiency are perhaps as common as deaths from acute coronary occlusion. The medical examiners of the City of New York and Newark, New Jersey, are of the opinion that in sudden unexpected deaths, acute coronary insufficiency is observed even more frequently than is acute complete obstruction.<sup>63</sup> Moreover, it should be kept in mind that the non-fatal cases of acute coronary insufficiency far outnumber the non-fatal cases of acute coronary occlusion. Simple episodes of angina pectoris fall in the former category. Even a severe form of the disease, accompanied by myocardial necrosis, culminates in death far less frequently than does acute coronary occlusion.<sup>38</sup>

#### CORONARY DISEASE AND INDUSTRY

It is appreciated today as never before that industry has a special interest in acute coronary artery diseases. In June, 1946, nearly 57,000,000 persons were employed in this country.<sup>64</sup> In New York State alone \$61,000,000 is paid out yearly<sup>65</sup> in claims arising from employment; and in the United

States as a whole, compensation claims for the year 1943 amounted to \$360,000,000.

Coronary artery disease plays no minor rôle in the field of compensation insurance. Indeed, the chronological relationship between work and an acute coronary episode is so dramatic that it is often assumed that every type of acute coronary disease is precipitated by exertion, excitement or trauma. This assumption is true as far as attacks of acute coronary insufficiency without acute occlusion are concerned. It is so evident that it may be accepted as a matter of fact. Existing controversy is concerned with the causation of acute coronary occlusion. As I have already stated, this condition is, in my opinion, an end result of long standing sclerosis of the coronary arteries and its onset cannot be attributed to any factor in the external environment, with the possible exception of shock and fall in blood pressure.

There would be less discussion and more agreement concerning the precipitating factors of acute coronary disease were it generally realized that there are two main acute coronary artery diseases, each distinct clinically and electrocardiographically from the other, but both due to a common underlying anatomical predisposing condition, namely, arteriosclerosis. Because exertion, excitement or trauma can cause acute coronary insufficiency,<sup>66</sup> this disease is definitely compensable among workers. Acute coronary occlusion, however, is a sequel of arteriosclerosis and is not precipitated by effort or excitement,<sup>2</sup> and therefore is not compensable.

The part played by effort, occupation and trauma in precipitation of acute coronary artery occlusion will be discussed in turn.

*Rôle of Effort in Acute Coronary Occlusion.* First, let us consider effort as a precipitating factor. My colleagues and I determined the events associated with the onset of 1,068 attacks of acute coronary occlusion by obtaining a detailed history of the activities

of the patient immediately prior to the attack and during the preceding hours, days and weeks.<sup>2</sup> The results are given in Table III. Fifty-two per cent of the attacks occurred

TABLE III  
TYPES OF ACTIVITY AT ONSET OF CORONARY OCCLUSION  
(1,068 ATTACKS)

	PER CENT
Sleep.....	22.5
Rest.....	29.5
Ordinary mild activity.....	21.0
Moderate activity (except walking).....	9.0
Walking.....	16.0
Unusual or severe exertion.....	2.0
Total.....	100.0

while the patient was asleep or resting; 21 per cent, during mild routine activity; 16 per cent, while walking; and 9 per cent, during moderate activity, such as pressing, painting and baking. In only 2 per cent of the cases was a history of unusual physical exertion obtained: Since these activities were engaged in by the patients for the portions of the day ordinarily spent in such pursuit, they must be ruled out as factors in the onset of occlusion. For example, almost half of the day is usually occupied in sleep or rest, and therefore the occurrence of half of the attacks during these states must be considered coincidental. The same inference may be drawn from the percentage for mild and moderate activity, as well as from the figure for unusual exertion, which preceded the attack in only 2 per cent of the cases. Even when a person guards against undue exertion some action requiring severe effort is usually performed during the day. Consequently, if effort were a factor in precipitating coronary occlusion the two would be associated much more frequently than they are and occlusion would be much more common than it is. In this connection it is worth noting that because of chronic illness, such as heart failure, cancer and surgical complications, at least seventy-five of the patients had been confined to bed for considerable periods prior to the occurrence of the occlusion.

*Rôle of Occupation in Acute Coronary Occlusion.* There have been conflicting reports concerning the relation of occupation to coronary occlusion. Some authors believe that coronary occlusion occurs most commonly among the laboring classes, whereas others have stated that it is more frequently observed among persons engaged in sedentary occupations and among business and professional people.

In a series of 1,268 cases in which we studied this factor, coronary occlusion occurred with equal frequency in all occupational groups.<sup>67</sup> In order to compare our occupational distribution with that of the general population as given by the U.S. Census, we divided our cases into three groups: workers and laborers, store, office and business men, and professional persons. We found that the ratios were almost identical with those for the general population of New York City. For instance, the first group comprised 51 per cent of our series and 55 per cent of the population; in the second group, the figure was 37 per cent, for both; the third group was 12 per cent in our series and 8 per cent of the population. Such close correspondence between the percentages eliminates occupation as a predisposing factor in coronary occlusion. Were coronary occlusion precipitated by effort, the incidence of strenuous occupations should be greater than that obtained in our series. Actually the percentage of sedentary persons was the same as that of heavy laborers.

*Rôle of Trauma in Acute Coronary Occlusion.* Attempts have been made to prove a causal relationship between trauma and coronary occlusion, but examination<sup>68</sup> of the published report on the subject reveals that many of the cases cited as trauma were caused by contusion of the heart and not by coronary occlusion. Indeed, in most instances the authors failed to differentiate the two conditions. In some of the cases reported postmortem examination was not made; the

presence of coronary occlusion was simply assumed despite the fact that the clinical similarity of the two conditions is marked. In certain other acute cases in which coronary occlusion was known to be present, not only had a long interval elapsed between the occurrence of the trauma and death, but there was pre-existing severe acute coronary artery disease, two facts that would suggest that the occlusion was not related to the trauma. From our study of reported cases and from our own experience we have been led to conclude that available evidence does not support the theory of causal relationship between trauma and classical acute coronary occlusion. On the other hand, trauma, direct and indirect, to the chest and even to the abdomen can produce arrhythmias and damage to the heart. It is, of course, conceivable that a severe injury could contuse a coronary artery with resulting closure of the lumen and infarction of the ventricle wall. However, an accident of this type would happen very rarely.

The rôle played by trauma in the initiation of coronary occlusion requires much more careful and critical investigation than it has received. Too often doubtful cases in the literature have been accepted as proved and cited as such by subsequent writers. The effect on the heart of trauma produced for experimental purposes is sometimes cited as proof of association of injury and acute coronary occlusion despite the fact that in such experiments contusion of the heart, not acute coronary occlusion, is produced.

*Outlook for Patients Following Recovery from Acute Coronary Occlusion.* The question as to whether or not patients should return to work following an attack of acute coronary occlusion is of practical importance both medically and economically. If he may return, how soon is it permissible to do so? Is it true, as some physicians believe, that return to work leads to further acute coronary occlusion and heart failure? These

questions are also significant from the standpoint of compensation insurance. Many persons possess disability policies and it has been assumed that acute coronary occlusion always indicates permanent and total disability. Positive answers to these questions cannot be given in the present state of our knowledge, but for many years I have urged that a more hopeful outlook should be adopted than that usually taken. Eleven years ago I found that fifty-three of seventy-five private patients had resumed their original work after recovery from an occlusion; only 8 per cent were completely disabled.<sup>69</sup>

Detailed follow-up data on 422 private and ward patients who had recovered from an attack of acute coronary occlusion is now available.<sup>67</sup> These patients came from all strata of society and were observed for intervals varying from six months to fifteen years, the average period being three and one-half years. Twenty per cent were followed five years or more. The ratio of men to women was 4½ to 1. Almost 90 per cent were in the age group forty to sixty-nine years, the sixth decade predominating. Three-quarters of the patients were seen in their initial attack, and almost all the others in their second.

Fifty-three per cent of the patients returned to work after recovery from the attack, 92 per cent of these doing so within one year. Actually, one-half resumed their occupations within three months after discharge from the hospital and three-quarters did so within six months. In the majority of cases, the work was full-time. The percentage of those returning to work was greater among the private patients than among the ward patients. Sex did not play a rôle in this respect.

There was a close correlation between resumption of work and age; the younger the patient, the more likely he is to return to work. In our series, 73 per cent of those in

the fourth decade resumed work, whereas only 43 per cent of those in the seventh decade did so.

Presence of previous attacks had a significant influence on rehabilitation following coronary occlusion. Fifty-nine per cent of the patients suffering a first attack resumed work; whereas only 38 per cent of the patients who had a second attack, and 23 per cent of those who had a third attack did so. Each successive attack reduces the probability of return to work; although one patient was able to work again following a fourth attack.

In our series only half the laborers resumed their occupations; two-thirds of the white-collar and office workers and four-fifths of the professional persons returned to work. The majority of those engaged in professions were able to work full time, whereas half of those in other occupations worked only part time. This difference in ability to resume work is more apparent than real since persons engaged in professional and executive pursuits can do relatively light work even on a full-time basis. In addition, they usually have a greater incentive to take up their occupations again.

As was to be expected, many of the patients who returned to work complained of such symptoms as weakness, precordial pain and dyspnea. This was true of about half the group, particularly the laborers, white-collar workers and housewives. However, their symptoms were not severe enough to preclude work; indeed, in many of these patients similar symptoms were present before the attack.

A considerable group ceased to work on the advice of their physicians or because they possessed disability insurance; some patients naturally were unable to find positions. We believe that a considerable proportion of this group would have resumed work had it been necessary. It is probable that in our entire series well over 60 per cent of the patients recovered suffi-

ciently to take up their customary occupations again had they wished to do so.

Evidence gathered from observation of 1,068 attacks of coronary occlusion indicates that the onset of an attack is not related to external factors such as effort, work or trauma; nor is it confined to any particular occupation or social strata. Coronary occlusion is the end result of a progressive atherosclerotic process and occurs as often in the sedentary individual as in one engaged in active work.

Our findings also indicate that an attack of acute coronary occlusion without complications is not in itself a reason for permanent or total disability. We believe that the outlook for a patient following recovery from an attack of coronary occlusion may justifiably be regarded more hopeful than in the past.

#### COMMENT

With the exception of isolated instances in which differentiation may be difficult, acute coronary insufficiency and acute coronary occlusion can be diagnosed as readily as can acute appendicitis. In the latter disease, diagnosis may occasionally prove troublesome. Thorough understanding of the clinical and electrocardiographic characteristics of the coronary diseases will enable the clinician to specify the type of acute coronary diseases present in almost every case. Naturally the clinical picture of the two types of acute coronary insufficiency will overlap at times. Occasionally, acute coronary insufficiency will cause acute myomalacia which is confluent and extends through from endocardium to pericardium, simulating acute coronary occlusion. This condition may arise when sclerosis of the coronaries is very severe and long standing.

Some writers<sup>49,70</sup> have been prompted to discard the term coronary occlusion on the assumption that it is impossible clinically to differentiate acute coronary occlusion with

infarction from acute coronary insufficiency with focal necrosis or infarction, but without acute occlusion. They consider that the term coronary occlusion should be confined to postmortem reports. I do not agree with this point of view, for, in my experience, acute coronary occlusion presents characteristic clinical and electrocardiographic changes which are almost always distinguishable from those produced by infarction caused by acute coronary insufficiency in which acute occlusion is not present.<sup>38</sup>

Acute coronary occlusion is to my mind a valuable diagnostic term. Not only does it embrace a typical syndrome, well known to every physician, but it is associated with a characteristic, progressive electrocardiographic pattern. The fact that in some cases acute coronary occlusion does not produce characteristic electrocardiographic changes, should not militate against the use of the term. In most cases of this type the electrocardiogram had been previously abnormal as a result of old coronary occlusion, bundle branch block, or marked enlargement of the heart, and the advent of another acute occlusion or of myocardial necrosis without acute occlusion may not alter the electrocardiogram significantly, or may produce equivocal or non-specific changes. In such cases the presence of a precipitating factor, such as effort, emotion, shock, operation or hemorrhage, should suggest acute coronary insufficiency without acute occlusion. The diagnosis can be made if the clinical picture of this condition is present, i.e., the pain not infrequently is mild, pericardial rub is absent and heart failure usually is not severe. Fever, leukocytosis and rapid sedimentation time are, as a rule, less marked than in acute coronary occlusion.

The concept of angina pectoris has undergone considerable change in recent years. It is now generally agreed that the attack represents temporary insufficiency of the coronary flow, and it has been suggested, therefore, that the term angina pectoris be

discarded, and another, such as transitory acute coronary insufficiency, be employed. Theoretically this change would be justified. However, the classical syndrome of angina pectoris, including the typical substernal pain and its radiation, its relation to effort, excitement, cold, and eating, and its relief by rest and nitroglycerin, is so characteristic and firmly established that it would seem advantageous to retain the term to connote acute coronary insufficiency without myocardial involvement.

#### SUMMARY

Acute coronary artery diseases have existed for hundreds, probably thousands of years. The arteriosclerosis observed in Egyptian mummies was of the same nature as is this disease today. Descriptions in the Bible are suggestive of attacks of acute coronary occlusion. Hippocrates is quoted as saying that "Cardiodynia, which occurs more frequently in senility, foretells sudden death." However, present knowledge of acute coronary occlusion became established only after the reports by Herrick in 1912 and 1918.

Heart disease has, since 1912, been the chief cause of death in this country. Four to eight million people suffer from heart diseases. Coronary disease comprises from 25 to 50 per cent of all heart diseases. With the lengthening span of life and therefore an increasing older population, the number of victims will continue to increase in the future.

There are two main divisions of acute coronary artery diseases: (1) Acute coronary occlusion, and (2) acute coronary insufficiency (myocardial necrosis or myomalacia or myocardial infarction without acute coronary occlusion).

Acute coronary occlusion denotes sudden complete closure, a sequel of progressive arteriosclerosis. The attack is not related to effort and excitement. It takes place during sleep and rest and routine

activities of the individual. The symptoms and signs are crushing substernal pain, not relieved by nitroglycerin, nausea and vomiting, shock, fall in blood pressure, change in heart sounds, gallop rhythm, fever, leukocytosis and increased sedimentation rate. The illness is prolonged and usually results in permanent changes in the heart. At autopsy the lumen of the coronary artery is found completely closed. The infarct is large, usually extending from endocardium to pericardium. The electrocardiogram is specific.

In acute coronary insufficiency (without acute occlusion) the severity of the disturbance varies from the simple short episode of angina pectoris, in which the pain is momentary, to the more severe type in which the anoxia of the heart muscle is prolonged, so that a serious injury to the heart muscle may take place. The episode is often related to exertion, excitement and emotion; it may occur after sexual intercourse, straining at stool or following gastroenteritis; it may be induced by extremes of heat and cold, tachycardia, auricular fibrillation, auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of any type, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism, hypothyroidism, etc. In a severe episode the heart muscle may contain many focal disseminated areas of subendocardial necrosis. These are often observed in the papillary muscles, but the endocardium and pericardium are not involved. The electrocardiogram discloses depression of the RS-T segments and T wave inversions which are characteristic. The prognosis of acute coronary insufficiency without acute occlusion is usually better than that of acute coronary occlusion with infarction. The former disease is compensable, the latter is not.

The treatment of these two types of acute coronary diseases differs. A rational existence and avoidance of the known pre-

cipitating causes prevent acute coronary insufficiency. Administration of digitalis, diuretics, quinidine, blood transfusions, etc., are of value in preventing acute changes in the heart muscle. In acute coronary occlusion, on the contrary, avoidance of predisposing factors does not prevent the onset of the attack. The best treatment of this is passive. Direct measures should be employed only if there are complications.

The distinction between acute coronary insufficiency and acute coronary occlusion is confused by careless use of terms. If the expression "myocardial infarction" is used as a diagnosis the qualifying phrases "with acute occlusion" or "without acute occlusion" are essential to accurate terminology.

There is evidence that the number of instances of acute coronary occlusion may be as high as 1,000,000 attacks per year. This means that one man in thirty and one woman in ninety, forty years of age and over, in this country annually sustain an acute obstruction of a coronary artery.

The incidence of acute coronary insufficiency is of the same magnitude and significance as that of acute coronary occlusion. In fact, in case of acute, sudden, unexpected death, acute coronary insufficiency is observed more frequently than is the acute complete obstruction.

Coronary disease is of great importance to industry. Nearly 60,000,000 people are employed in this country. Hundreds of millions of dollars are paid out yearly in compensation disability benefits.

Trauma, direct and indirect, can produce arrhythmias and damage to the heart. It very rarely if ever causes an acute coronary occlusion with infarction. In a severe steering wheel, or similar accident, with bruise of the chest wall and contusion of the wall of the left ventricle, an occlusion may rarely take place.

Evidence gathered from observations of

more than 1,000 attacks of acute coronary occlusion indicate that the onset of the attack is not related to external factors such as effort, work or trauma, nor is it confined to any particular occupation or social stratum. Acute coronary occlusion is the end result of an arteriosclerotic process and occurs as often in a sedentary person as in one engaged in active work.

Fifty-three per cent of patients return to work after recovery from the attack of acute coronary occlusion, nearly all of them within the first year. The younger the patient, the more likely is he to return to his employment. Each successive attack of acute coronary occlusion reduces the probability of return to work. Only half the laborers resumed their occupations, whereas two-thirds of the white collar and office workers, and four-fifths of the professional persons returned to their jobs.

Our findings thus indicate that an attack of acute coronary occlusion is not in itself a reason for permanent disability. We believe that the outlook for a patient recovering from an attack of acute coronary occlusion may justifiably be regarded more hopefully than it has been in the past.

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## Diagnostic Value of Roentgenography and Fluoroscopy in the Diagnosis of Rheumatic Heart Disease\*

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ROENTGENOGRAPHY and fluoroscopy of the heart have been widely used for many years in the diagnosis of rheumatic heart disease. The method is valuable in conjunction with physical examination, electrocardiography and various laboratory procedures, but may be misleading if considered apart from the other procedures. My approach has at all times been that of the clinician trained in the use of this tool rather than that of the roentgenologist with a knowledge of heart disease.

The value of this method in rheumatic heart disease might be discussed under the following headings: (1) The value of roentgenology in arriving at an etiological diagnosis; (2) roentgenology in the estimation of anatomical sites of lesions; (3) the roentgenological manifestations of rheumatic activity; (4) roentgenology as an aid in estimating the age or duration of cardiac involvement; and (5) the clinical correlation between signs and symptoms and their roentgenological manifestations.

### VALUE OF ROENTGENOLOGY IN ARRIVING AT AN ETIOLOGICAL DIAGNOSIS

There are a number of conditions which at times may produce an image, particularly

in the postero-anterior view, which simulates that seen so frequently in rheumatic cardinals. A prominent pulmonic segment is not unusual in thyrocardiacs, and a straightening of the left upper cardiac contour occurs in chronic cor pulmonale, right heart failure secondary to left-sided failure, in congenital heart disease, and other disorders. Figure 1A shows a heart in the postero-anterior view triangular in shape, with a straightened left upper cardiac contour. The original report of the roentgenologist suggested "mitralization." This proved to be a case of chronic cor pulmonale secondary to bronchial asthma, emphysema and bronchiectasis. The right anterior oblique view (Fig. 1B) shows a bulge into the upper retrosternal space, while the course of the barium-filled esophagus indicates that the left auricle is not enlarged. The left anterior oblique view (Fig. 1C) shows a small left ventricle, a marked grade of inflow tract enlargement of the right ventricle, and enlargement of the right auricular appendix. It is obvious that the appearance in the postero-anterior view is not at all diagnostic; indeed the initial report was actually misleading.

There really is no typical roentgenological picture in rheumatic heart disease. In

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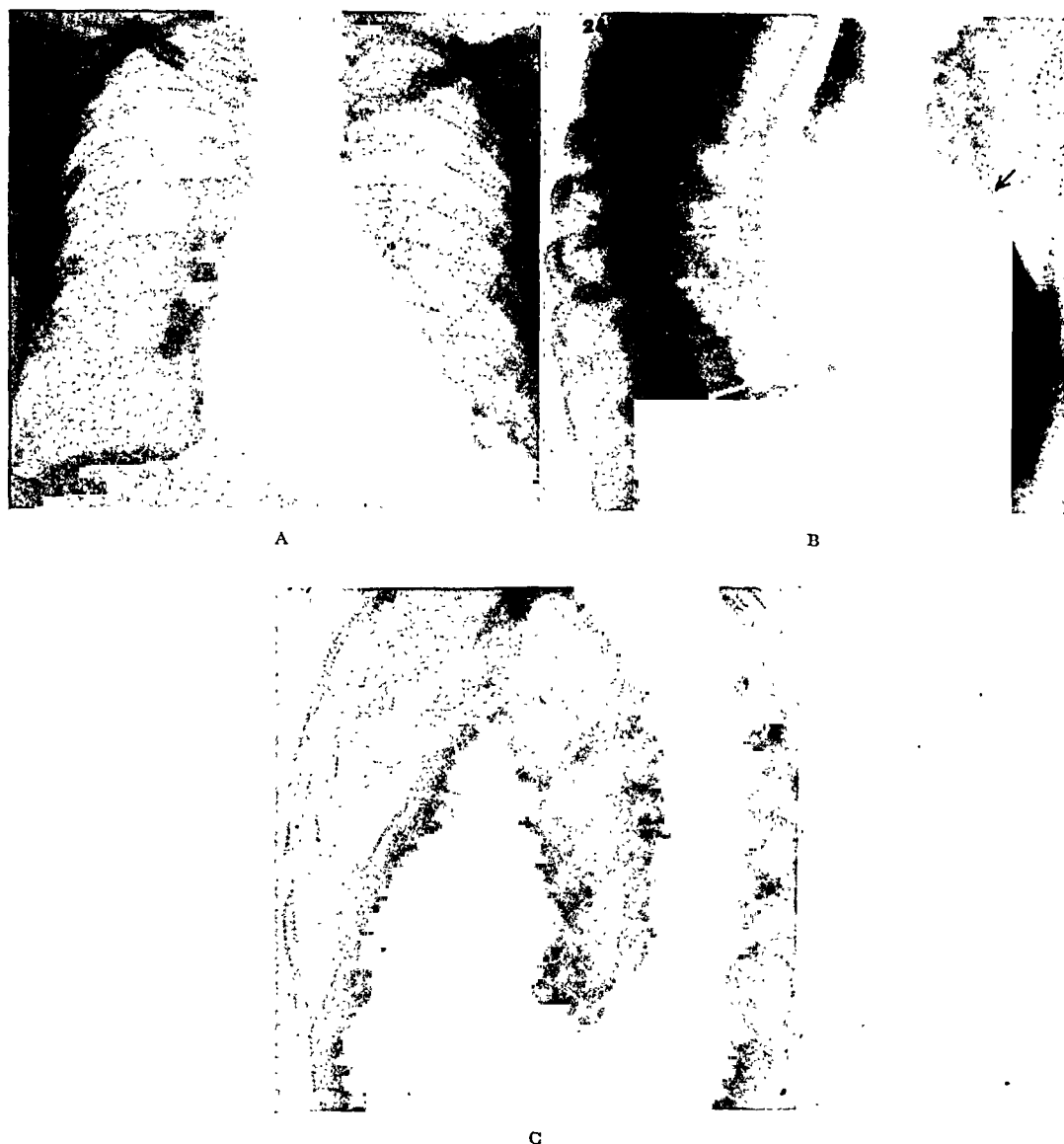


FIG. 1. A, B, C, roentgenographic illustrations from a case of chronic cor pulmonale.

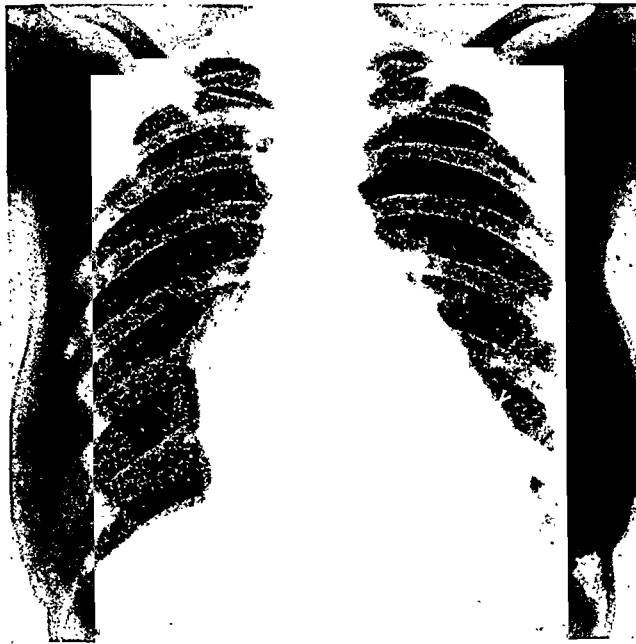
response to various kinds of damage there is cardiac chamber enlargement involving one, two or even all chambers. The frequently associated enlargement of the left auricle and the right ventricle occurs often in mitral valvular disease. However, it is the association of enlargement of the various individual chambers that is suggestive rather than the overall shape of the heart. A diagnosis of mitral valvular disease based on auscultatory findings is justified even in the absence of left auricular or right ventricular enlargement. Many such instances were found in examination of

selectees for induction into the armed services.

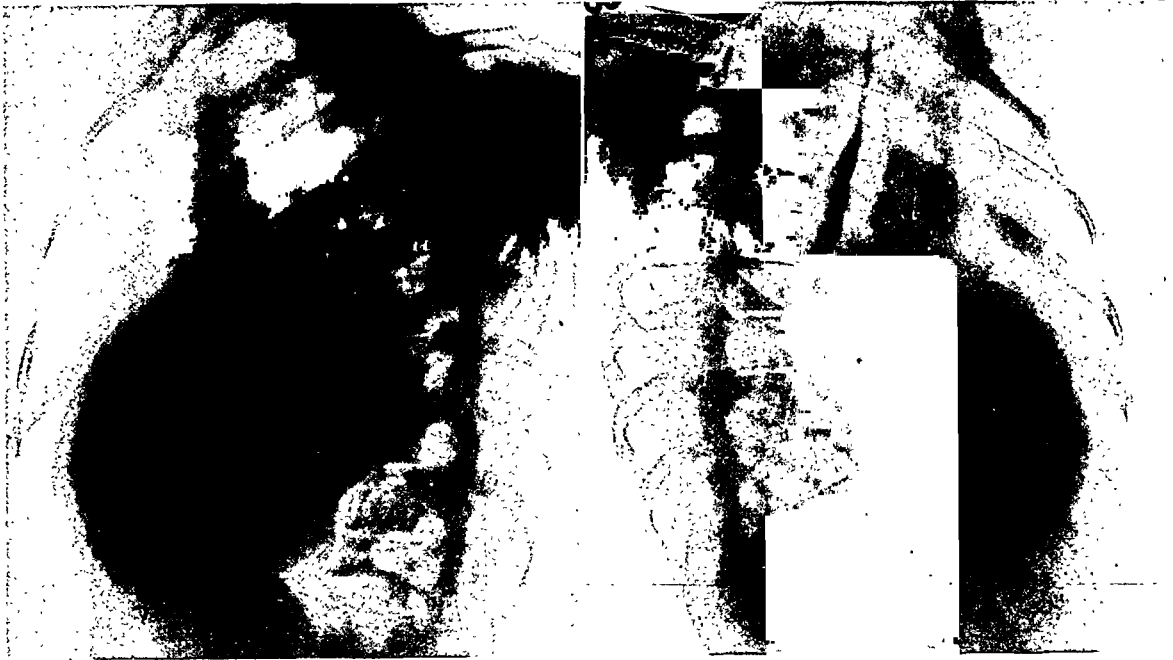
#### ROENTGENOLOGY IN THE ESTIMATION OF THE ANATOMICAL SITES OF LESIONS

Here recognition of individual chamber size is important. This is determined chiefly by fluoroscopy, while roentgenograms in the postero-anterior and in the right and left anterior and in the right and left anterior oblique positions are confirmatory, and give us a permanent record useful for comparison with subsequent examinations.

The left ventricle may be enlarged in



A



B

C

FIG. 2. A, B and C, roentgenographic illustrations from a case of rheumatic heart disease with mitral stenosis and tricuspid incompetence. "X" marks the point of opposite pulsations.

mitral insufficiency and in aortic valvular disease. The grades of enlargement vary considerably. Aortic insufficiency may be associated with marked left ventricular enlargement, slight enlargement, or none at all. Mitral insufficiency on the other hand often causes no left ventricular enlargement,

and when enlargement does occur it is usually slight or moderate in degree. In mitral stenosis the left ventricle is usually not demonstrably enlarged. Enlargement of the heart shadow to the left in such instances is due to the displacement of a small left ventricle to the left by right

ventricular enlargement. Figure 2A is the film of a young woman with mitral stenosis and tricuspid incompetence. Note the size of the left ventricle below the point of opposite pulsations marked "X." There is no elongation or rounding of this left ventricular segment, and in the left oblique view (Fig. 2B) there is no left ventricular bulge backwards or down. In the postero-anterior view (Fig. 2A) there is straightening of the left upper cardiac contour and a diminution in the size of the aortic knob. A double density is noted on the right due to an enlarged left auricle. In the left anterior oblique view (Fig. 2B) note, too, that the left auricle is large enough to have elevated and compressed the left main bronchus, that the inflow tract of the right ventricle is enlarged and that the right auricular appendix segment is elongated. The right anterior oblique view (Fig. 2C) demonstrates retrosternal bulge and left auricular enlargement.

To sum up: The left ventricle is not enlarged but is displaced to the left by right ventricular enlargement. The left auricle, the right ventricle and the right auricle are enlarged to a considerable degree. These findings served to corroborate the physical findings.

A boy with mitral valvular disease presented a long, loud, mitral systolic murmur but no diastolic murmur was heard. The left ventricular segment (Fig. 3A) below the point of opposite pulsation marked "X" is rounded and elongated. In the left anterior oblique view (Fig. 3B) the left ventricular segment is moderately enlarged. In this view, too, the left bronchus is elevated and compressed by an enlarged left auricle; the right auricle and inflow tract of the right ventricle are enlarged. The left auricle is greatly enlarged in the right oblique view (Fig. 3C), displacing a barium-filled esophagus posteriorly.

Finally, here is a third variant in left

ventricular size, in a young man with rheumatic aortic insufficiency plus either mitral incompetency or mitral insufficiency. The left ventricle is greatly enlarged, the left auricle only slightly so, the other chambers are within normal limits, while the ascending aorta is elongated and dilated. The amplitude of left ventricular and aortic pulsations was increased, in conformity with the high pulse pressure and other Corrigan manifestations present in this case.

To sum up on the determination of anatomical sites of lesions: Various grades of chamber enlargement are associated with individual valvular lesions and with altered dynamic output.

It is possible to demonstrate calcified valves, especially when sought for actively, also calcification of the pericardium. Demonstration of systolic expansion of the left auricle indicates mitral insufficiency. Observation of expansile pulsations of the hilar arteries, termed "hilar dance," establishes pulmonary valvular insufficiency or incompetency.

#### ROENTGENOLOGICAL MANIFESTATIONS OF RHEUMATIC ACTIVITY

The appearance and regression of a pericardial effusion in rheumatic cardiacs is generally acknowledged as evidence of rheumatic activity. It is also generally conceded that cardiac enlargement in rheumatic heart failure is due to active carditis. It is my belief that progressive cardiac enlargement, or the demonstration of individual cardiac chamber enlargement when compared with a previous examination even in the absence of congestive failure, is also an indication of rheumatic activity. This is true whether such enlargement is or is not associated with the usual manifestations of congestive heart failure. The chambers that are most frequently enlarged in rheumatic heart disease are the left auricle

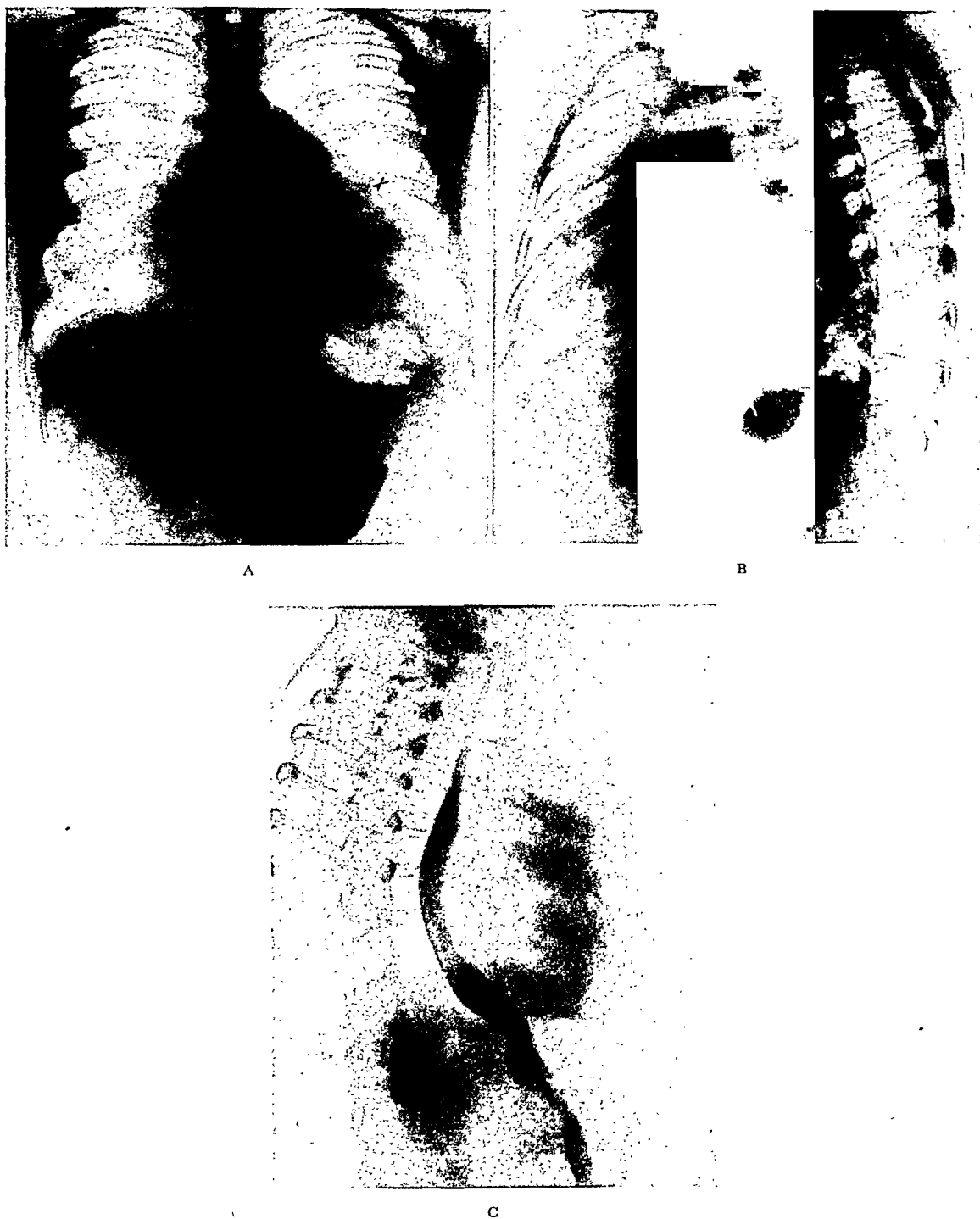


FIG. 3. A, B and C, roentgenographic illustrations of a case of rheumatic heart disease with mitral insufficiency. "X" marks the point of opposite pulsations as noted during fluoroscopy.

and the right-sided chambers, though not necessarily in equal degree. Here, however, was an instance in which the only manifestation of rheumatic activity, as far as I could determine, was in cardiac enlargement. Figure 4A is the film of a young woman with

mitral stenosis. Fluoroscopy at this time showed a prominent conus segment in the postero-anterior as well as right anterior oblique views, no right ventricular inflow tract enlargement, but slight left auricular enlargement. She seemed perfectly well

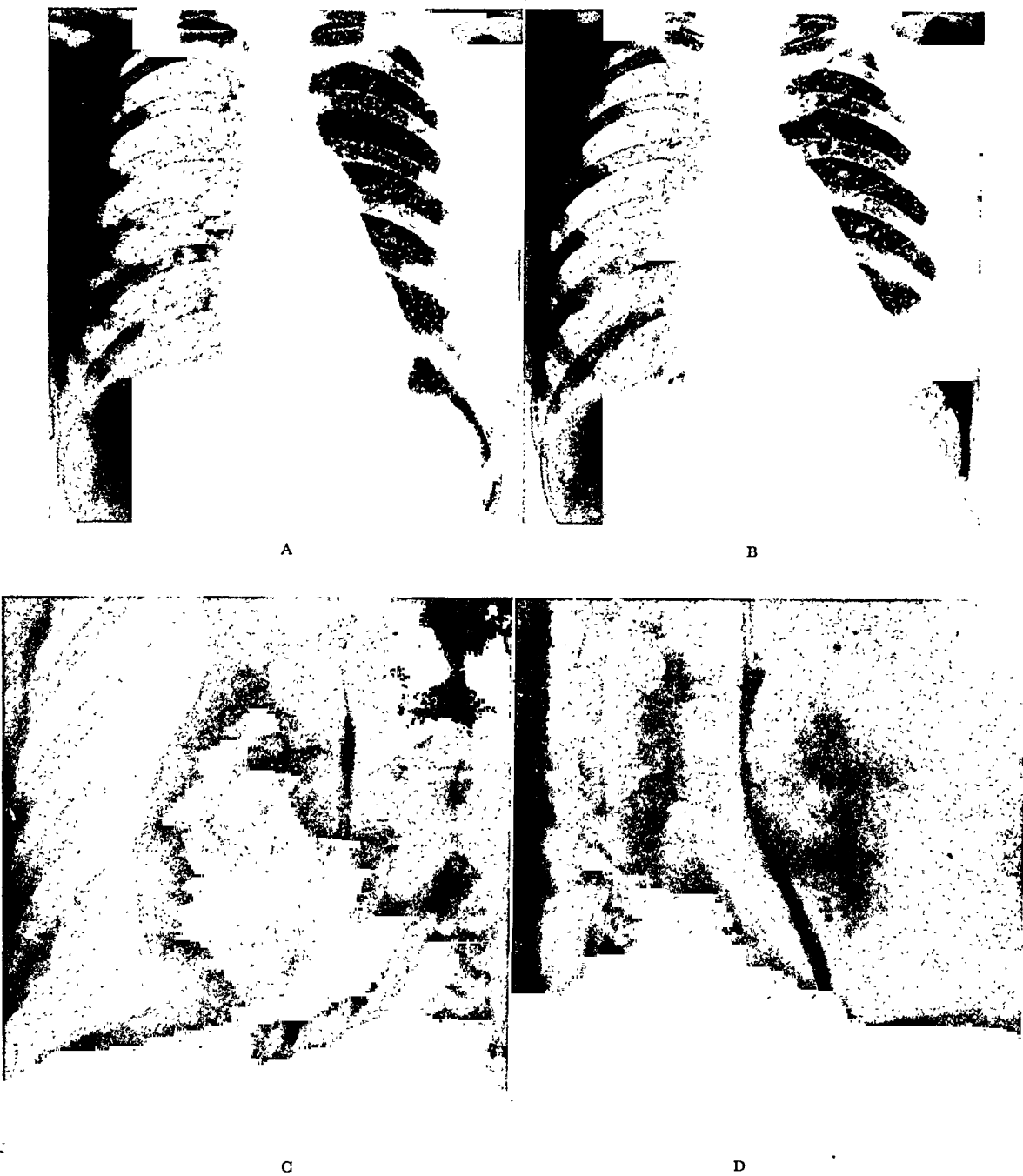


FIG. 4. A, B, C and D, cardiac enlargement as the only manifestation of rheumatic activity.

compensated, performed moderately strenuous duties without breathlessness or discomfort. Two years later (Fig. 4B) significant increase in cardiac size was noted. The left anterior oblique view (Fig. 4C) shows no significant right ventricular inflow tract enlargement, though a comparison film unfortunately is absent. The right oblique view (Fig. 4D) demonstrates moderate

retrosternal bulge and slight left auricular enlargement.

At this point this girl was thoroughly rechecked. There was no change in her auscultatory findings. Her appetite and weight were unchanged. Her white blood count, differential count and sedimentation rate were within normal limits. Electrocardiograms failed to reveal any of the usual

criteria for rheumatic carditis. She had married and led an active social life including dancing and bicycling, in addition to her work.

On the basis of the roentgenological examinations, however, she must be regarded as having an active though smoldering type of rheumatic carditis. It might be argued that purely mechanical stress might have caused such enlargement. Against this are the numerous observations on other supposedly healed rheumatic cardiacs, subjected to similar physical stresses, who do not develop such cardiac enlargement. I therefore regard this patient, and others with similar cardiac chamber enlargements, even in the absence of the usual criteria for rheumatic carditis, as cases of rheumatic activity.

While on this point of rheumatic activity it might be well to mention that demonstrable calcification of a mitral or aortic valve, or calcified pericarditis, probably indicates cessation of rheumatic activity in at least the involved calcified areas. Other areas, however, may be the sites of active carditis in the same patient. (Fig. 5.)

#### ROENTGENOLOGY AS AN AID IN ESTIMATING THE AGE OR DURATION OF CARDIAC INVOLVEMENT

Valvular or pericardial calcification is a late manifestation in rheumatic heart disease. I have never found them before eight or ten years after the onset of the initial episode of rheumatic fever, this in spite of the fact that calcium deposition may occur within a matter of weeks or months. While on this point of calcification it might be well to discount the prevalent notion that calcified pericarditis is rarely rheumatic. It just isn't so. I know of four definite cases of calcified pericarditis in rheumatic cardiacs, three proven at autopsy, the other shown during life. (Fig. 5.)

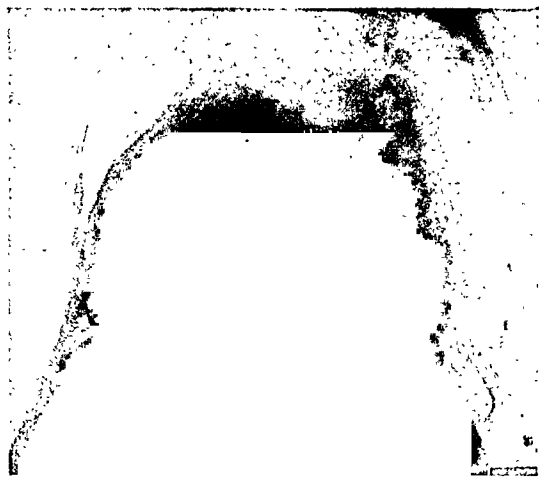


FIG. 5. Calcified pericardium (see arrow) in a young woman with rheumatic heart disease, mitral, aortic and tricuspid valvular enlargement.

Pulmonary fibrosis of the stippled variety, simulating miliary tuberculosis and at times also silicosis, is a late sequel of chronic recurrent pulmonary congestion in cases with rheumatic mitral valvular disease.

An interesting and an important aid in estimating the age of cardiac involvement is the finding of elevation and compression of the left main bronchus by an enlarged left auricle. Compression of the bronchus can occur only while the bronchial cartilage is soft and pliable, that is not beyond the teens. Elevation of the left bronchus without compression, however, may occur beyond that age. The finding of a compressed and elevated left main bronchus, therefore, indicates that left auricular enlargement occurred at or before the patient was fifteen, carditis often being unknown to the patient.

#### CLINICAL CORRELATION BETWEEN SIGNS AND SYMPTOMS AND THEIR ROENTGENOLOGICAL MANIFESTATIONS

Patients with left ventricular enlargement, even of marked degree, may be completely or relatively asymptomatic. There have been athletes of considerable renown with aortic insufficiency and significant left ven-



tricular enlargement. Left auricular enlargement, due to mitral valvular disease or to mitral valvular incompetency with left ventricular enlargement, may be associated with pulmonary manifestations which vary considerably in degree. The occurrence of pulmonary congestion is usually accompanied by right ventricular enlargement. Enlargement of the right ventricular inflow tract and the right auricular appendix is usually associated with venous and hepatic engorgement, dependent edema, diminished blood flow to the pulmonary circulation, and in consequence there is a diminution in pulmonary congestion.

While on the point of correlation between signs and symptoms and roentgenological manifestations, it might be well to re-emphasize a point made previously, namely, that organic valvular disease may be present in the total absence of any cardiac chamber enlargement. I found hundreds of such instances while examining selectees for induction into the armed services, not only those with indubitable mitral valvular disease, but also many with aortic insufficiency. However, I recall no instance of aortic insufficiency with a high pulse pressure that was not associated with left ventricular enlargement.

The roentgenologic pulmonary manifestations of rheumatic disease may be classified as follows: (1) Pulmonary congestion, vascular and interstitial; (2) pleural effusions, general, loculated and interlobar; (3) pulmonary infarction; in cardinals the latter is the most frequent cause of pulmonary densities, occurring more often than intercurrent pneumonic infections. Pulmonary infarction should be sought for not only when there are chest pains, fever and hemoptysis, but also when there are manifestations of collapse, pallor and cold sweats, or when the patient develops slight unexplained temperature elevations, or fails to respond to hitherto effective doses of digitalis

or diuretics. The differential diagnosis here should always include rheumatic activity and pulmonary infarction. (4) Acute pulmonary edema: The central densities radiating from the hila, which have at times been described as the pulmonary manifestations of uremia, will frequently be found during or shortly after episodes of severe paroxysmal dyspnea and in pulmonary edema. Similar densities occur in paroxysmal pulmonary hemorrhages. (5) Chronic pulmonary edema, resulting in small, irregular, dense areas, usually in the lower portion of both lung fields; at times in larger densities, involving a complete lobe or more, due to localized failure to evacuate interstitial and alveolar fluid. The densities of chronic pulmonary edema must be differentiated also from atelectasis, plate-like areas of pulmonary infarction, interlobar effusions and pneumonitis. (6) Rheumatic pneumonia: large, small or confluent densities associated with active rheumatic carditis; (7) pulmonary fibrosis, and (8) pleural thickening.

In conclusion it may be said that roentgenology is of considerable assistance to us in rheumatic heart disease in various ways; as in the determination of heart chamber size, in evaluating associated pulmonary phenomena and complications, and in the recognition of various affections of the pericardium and valves. I might stress once again that it is only one of the methods, an important one, used in heart disease and as such must be correlated with other laboratory procedures and with the physical examination. Failure to appreciate the limitations of this method of examination may cause the examiner considerable grief and chagrin.

#### DISCUSSION

DR. TARAN: Thank you, Dr. Schwedel. Your views fit in so well with some of the criteria for rheumatic activity that have

been evolved here at St. Francis Sanatorium. I am glad that Dr. Schwedel stressed that progressive cardiac enlargement is a manifestation of rheumatic activity rather than a result of mechanical stress caused by valvular defects. Are there any questions?

DR. ALLEN: Were the obliques taken with any sort of mechanical device to assure a proper angle of rotation?

DR. SCHWEDEL: No, these films were taken without any mechanical aids. I suppose a turntable or goniometer might be used once the degree of desired rotation has been established during fluoroscopy. There is no predetermined angle of rotation. The right auricular appendage is seen in its fullest extent in the earlier degrees of rotation into the left anterior oblique, and so is the ascending aorta. The left ventricle, however, may not be thrown clear of the spine, even in normal individuals until an angle of 60 to 65 degrees is attained. In the right oblique the optimum visualization of a retrosternal bulge as well as the retrocardiac projection of an enlarged left auricle will vary with each patient.

QUESTION: How do you differentiate between elevation and compression of the left main bronchus by an enlarged left auricle? Is there a definite pressure area?

DR. SCHWEDEL: In compression there is definite narrowing of the air-filled bronchus. Compression generally is associated with elevation of the bronchus, involving the entire bronchus, the central portion or the peripheral portion, or the elevation and compression may be arc-shaped.

QUESTION: Does the bronchial compression ever result in atelectasis?

DR. SCHWEDEL: I have never seen atelectasis attributable solely to bronchial compression. Bronchial narrowing, however, when associated with diaphragmatic elevation, pleural effusion or an intrabronchial mucous plug, may result in pulmonary

alveolar collapse, a term preferable to atelectasis.

QUESTION: Are the miliary-like accumulations in mitral stenosis a manifestation of chronic passive congestion of the lungs?

DR. SCHWEDEL: No, these accumulations represent the residual end process of previous episodes of cardiac failure; areas of alveolar collapse and interstitial fibrosis resulting in localized millet-sized areas of fibrosis, simulating the picture in miliary tuberculosis, miliary carcinoma, sarcoidosis or early silicosis. In patients with such a picture a superimposed passive congestion will tend to obliterate the sharp outlines of these miliary-like densities. In chronic passive congestion the picture is one of diffuse haziness, plus increase in the width of the hilar arteries.

QUESTION: How often do you find a calcified valve?

DR. SCHWEDEL: Seek and ye shall find. Fifteen years ago a calcified valve had to hit me in the face before I recognized it. Since then I have found many, chiefly because I have trained myself to look for them. They are most frequently discovered during fluoroscopy, with shutters constricted to a relatively small opening. Small or larger areas of increased density, moving up and down or in a rotary motion with each cardiac cycle, indicate valvular or annular calcification. At times they are exceedingly difficult to register on films even with a spot film device.

Here is a film showing calcification of the mitral valve. In this right oblique view notice this vertical row of calcifications within the heart density.

Look at the barium-filled esophagus. Note the displacement due to left auricular enlargement. If you look closely, above there is displacement of the esophagus anteriorly in the region of the aortic arch; in the postero-anterior position the aortic compression is from the right, instead of from

the left as is normal. This type of esophageal displacement is caused by right aortic arch. The association of mitral stenosis and right aortic arch may be sheer coincidence but might be due to an interauricular septal defect. She had no demonstrable left ventricular enlargement, a large left auricle, and a marked degree of right ventricular and right auricular enlargement, dilated pulmonary arteries; all findings consistent with this diagnosis. She died but an autopsy was not obtained.

DR. WATTS: What is the source of emboli in pulmonary infarction in rheumatic fever cases?

DR. SCHWEDEL: The cause of pulmonary infarction usually is embolic, though I have seen instances of *in situ* thrombosis of pulmonary artery branches obliterating the lumen completely or partially, some of which resulted in pulmonary infarction. When the source is embolic it may come from a distal source, such as the calf veins, also pelvic and lumbar veins or the emboli may originate centrally from within the heart, more frequently when auricular fibrillation is present, but often enough when there is a regular sinus rhythm.

DR. RUBIN: If all of the criteria are absent in specific cases, except for progressive enlargement of the heart, how long is it before you say that activity has ceased?

DR. SCHWEDEL: If on repeated observations, say at six-month intervals, there is no further enlargement, the supposition is that this manifestation of rheumatic activity has ceased. Since it is rather difficult to evaluate slight changes in size a final decision on size should not be made in less than, say, two years.

There is a possibility that rheumatic activity may exist without clinical, laboratory or roentgenographic manifestations. The postmortem observations of Drs. Kugel, Rothschild and Gross in rheumatic cardiacs indicate that rheumatic activity was present in almost all below thirty, and in approxi-

mately a fifth beyond the age of fifty. While this group was not representative, consisting as it did of cardiacs in failure, it suggests that evidence for rheumatic activity is frequently unrecognized. It would be interesting to have more data gathered on rheumatic cardiacs who died of causes unrelated to their heart disease, groups of cases available to City Medical Examiners or to coroners.

DR. BENJAMIN: Do you believe that a patient with marked valvular involvement but without rheumatic activity will develop cardiac enlargement?

DR. SCHWEDEL: Such a patient may go on for years without enlargement. I suppose belief in enlargement on a mechanical basis need not be discarded entirely, but modified to the extent that if stress is unusual and prolonged, or complicated by such factors as hyperthyroidism or coronary artery disease or some other such factor which puts an additional burden on the original mechanical difficulties, then cardiac enlargement may occur.

DR. BENJAMIN: How about the cases with considerable valvular deformity, do they develop enlargement over a period of years?

DR. SCHWEDEL: Mechanically, no. I believe that unless complicated by other factors cardiac enlargement in rheumatic cardiacs should be considered as a manifestation of rheumatic activity.

DR. BENJAMIN: How about cardiac enlargement in congenital heart disease?

DR. SCHWEDEL: In congenital cardiacs, as well as other non-rheumatic cardiacs, enlargement is probably the result of a combination of mechanical causes plus such systemic factors as hypoxia, relative diminution in blood supply with one capillary serving an increase in muscle mass, plus complicating factors such as infection.

DR. DOWD: How does the heart compensate for a tight mitral valve without hypertrophy or enlargement?

DR. SCHWEDEL: I suppose you are referring to the instances of mitral valvular disease rejected for the armed services that I mentioned previously. Because of presystolic murmurs they were termed mitral stenosis. I seriously doubt whether they actually had real obstruction to the flow of blood into the left ventricle. We have all used the term mitral stenosis too loosely, and the term mitral valvulitis with deformity is preferable and correct. These cases had no left auricular or right ventricular enlargement. True cases of mitral stenosis with obstruction have left auricular and right ventricular enlargement.

The left auricle and right ventricle may be enlarged disproportionately. Dr. Benjamin Gouley, of Philadelphia, has pointed out that the right ventricle may enlarge even in the absence of left auricular enlargement, this being secondary to rheumatic involvement of the lungs.

DR. TARAN: Dr. Schwedel, would you expand a bit on the advantages and limitations of fluoroscopy in the study of rheumatic heart disease?

DR. SCHWEDEL: A fluoroscope is practical, convenient and is for most purposes accurate, at least I think it is so in my hands. For comparison purposes I have worked out a simple method for the estimation of transverse diameters which works out pretty well. By narrowing the shutters to a vertical slit I indicate the right and left outlines on the patient's chest or abdomen with a skin-marking pencil. This diameter, plus sketched fluoroscopic outlines in the postero-anterior and both oblique positions, are drawn in smaller scale on the chart, and the degree of enlargement of each chamber and the aorta is indicated by plus or plus-minus signs. This method has served adequately for comparison, is convenient, inexpensive and about as

accurate as any of the other methods. For fine lung detail I send the patient out for a teleoroentgenogram.

DR. TARAN: How much reliance can be placed upon the angle of clearance as an aid in estimating the size of the left ventricle? If this angle of clearance over a period of time changed from 55 to 65 degrees would you consider this to be an indication of left ventricular enlargement?

DR. SCHWEDEL: I might consider the change to be due to an error in technic, and I believe errors are too frequent to make this method reliable as an index of left ventricular enlargement. Ten years ago, Dr. Harry Gross and I did a control series using this method, which included the use of a well constructed turntable, on about 160 school children. These were classified as to age, sex, weight and body build. The outlines were traced on cellophane and checked twice more. When the difference in all three checks was less than five degrees, the results were considered reliable and the figures averaged. We found no correlation between the angle of clearance and the size or shape of the heart. It seemed as if the varying factor was the distance between the posterior surface of the heart and the anterior contour of the spine.

Enlargement of the left ventricle results in increase in the length of its contour. Early such enlargement occurs downwards, or by increased rounding, termed a "fleshy" border by old-time roentgenologists. Later the enlargement involves the posterior portion, the inflow tract, which is the portion that is concerned in the angle of clearance. The only thing I will concede here is that a considerably enlarged left ventricle will usually fail to clear at an angle of 55 degrees, but by that time we do not need the angle of clearance to establish enlargement.

# Electrocardiographic Findings in Rheumatic Heart Disease\*

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I DO not believe that the electrocardiogram shows features that are characteristic effects of rheumatic fever alone and therefore would not afford criteria for the diagnosis. On the other hand, it is certainly true that there are many instances in which the electrocardiogram may give the only sign of rheumatic activity. This is more apt to be true at the end than at the beginning of an acute attack. I have seen patients in whom there were no joint symptoms and who had only electrocardiographic changes. I remember one such patient, who came into the clinic ambulatory, with fever and with electrocardiographic changes, and we did not quite know why. She then developed a pericardial rub, and the reason for the electrocardiographic changes became evident. She later developed some joint symptoms which led to a diagnosis of rheumatic fever. But that case I think is exceptional. Usually the electrocardiogram is a manifestation of the disease which is diagnosed on the basis of other findings.

Rheumatic fever, of course, is much more extensive a disease than the rheumatic myocardial involvement which gives rise to the electrocardiographic changes. There are many other areas where rheumatic fever may attack besides the myocardium. The electrocardiogram should be considered as giving evidence of changes in myocardial function, and in rheumatic fever these functional changes are caused by certain

types of pathological reaction to the rheumatic process.

There are in general three types of pathological changes: (1) There is a general inflammatory reaction with edema, interstitial swelling, leukocytosis and fibrinous degeneration. (2) There is the specific type of pathological change known as the Aschoff body, which is found in the interstitial tissue surrounding the small muscle bundles and particularly in the interstitial tissue surrounding the smaller arteries. (3) And then there is an arteritis which is also a definite rheumatic manifestation and which occurs in the coronary arteries as well as in other arteries of the body. We are particularly concerned with the coronary arteries where it causes an intimal thickening and eventually a fibrosis of the vessel wall.

Rheumatic endocarditis of itself probably does not affect the electrocardiogram, with the possible exception of that peculiar mural endocarditis occurring chiefly in the left auricle. This may give rise to auricular premature beats, auricular tachycardia and possibly, auricular fibrillation or flutter. Rheumatic valvulitis will not influence the electrocardiogram unless the valvular disease is severe enough to produce a mechanical change in the pressure in the ventricles, hypertrophy of one of the ventricles or auricles. The effects of myocardial disease upon the electrocardiogram, of course, depend upon the area of myocardium that

\* One of the Seminars on Rheumatic Fever conducted at St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, New York, October 30, 1945.

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is affected and on the character of the pathological change; that is, whether it results in irritation or a depression of the muscular tissue. The myocardial change is sometimes of a severe degenerative character though this is rare. The muscle fibers in such cases are degenerated and this produces a different type of electrocardiographic abnormality from that resulting from the usual inflammatory reaction with edema, infiltration and Aschoff bodies. Occasionally, the rheumatic arteritis may become so severe that it may occlude a coronary vessel and lead to thrombosis though this, too, is a rare occurrence.

Depending upon the effect on the muscle, we may find premature beats, paroxysmal tachycardia or other rhythm disturbances arising either in the auricles, the A-V node or in the ventricles. Actually, I am not aware that ventricular tachycardia has ever been observed in rheumatic fever though tachycardias with other foci have been repeatedly observed. Auricular fibrillation and flutter, and prolonged A-V conduction sometimes progressing to heart block with dropped beats or even to complete heart block may occur. Bundle branch block is a rare finding.

Certain changes in the QRS group and T wave may occur, such as low voltage of QRS, low voltage of T and changes in the electrical axis of QRS. There may be elevation of the S-T junction probably occurring as a result of acute degenerative changes and also diphasic or inverted T waves in leads I or II or both. These features usually are found during the active phase of the disease though they sometimes persist after other signs of activity have gone, even after the sedimentation rate has returned to normal.

Occasionally, changes in the T wave or in the P-R interval may persist after the disease has become inactive. It may be that in these cases there is fibrosis, which is

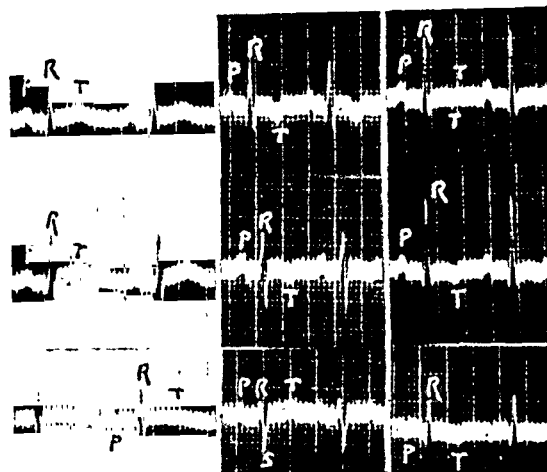


FIG. 1.

interfering with the function of the tissue. There is one interesting thing which has been observed about the A-V conduction time in rheumatic fever. Good-sized doses of atropin, such as might paralyze the vagus, will shorten the conduction time and this has been considered by some to indicate that a heightened vagus activity, an increased vagal tone, was responsible for the prolonged conduction time of rheumatic heart disease. This argument does not appeal to me because it is possible that the diseased tissue reacts abnormally to a normal vagal tone. The mere diminution of a vagal effect by atropin does not prove that the whole effect is due to the vagus.

Figure 1 shows records from three different patients. They all show a normal P-R interval; although in two of them it measures 0.20 second. There also is in the record on the left an elevation of the S-T junction. It is definitely elevated in leads I and II and very slightly in lead III. The patient had this electrocardiogram for a few days and then developed a pericardial rub, which did not surprise us because such S-T elevation is the recognized electrocardiographic sign of pericarditis. The central record shows nothing particularly significant in the QRS group except left axis deviation of slight degree, but the T wave is inverted in lead I,



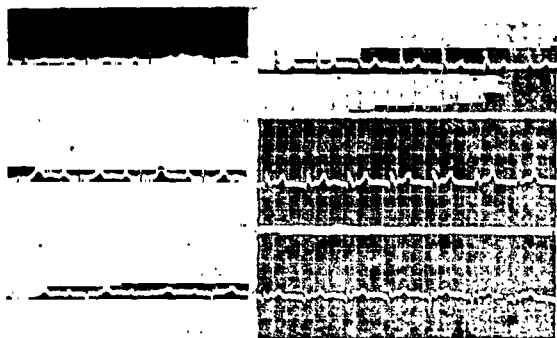


FIG. 4.

beats, or it may alternate with periods of regularly dropped beats. That is, there might be two auricular waves to one ventricular complex. It is not as high a grade of block as the two to one block and the characteristic thing is that it is transient. Clinically, it must be diagnosed from premature beats. This should be possible by noting the absence of any premature ventricular sound.

Figure 4 shows two records of a patient in the acute phase of rheumatic fever. The one on the left shows a prolonged P-R, which in lead I measures 0.24 second and in lead II 0.28 second, but in addition shows a low voltage of the QRS group, no wave being larger than R-2, which measures only 3.5 mm. In spite of this low voltage of QRS the T wave has a normal voltage, the largest amplitude being found in lead II where it reaches 3 mm. This same patient later developed a regular tachycardia with a rate of almost 100 per minute. No one suspected that there was anything but an ordinary sinus tachycardia, but the record seen on the right shows a nodal tachycardia to be present by the P wave which comes each time just after the QRS group. This is not an uncommon phenomenon in patients with rheumatic heart disease. I think it is more common than auricular tachycardia. You will notice that the T wave in these records is not abnormal in its form. There is one peculiar thing, however, seen in the second lead: the first, third and fifth T waves are larger than the second, fourth,

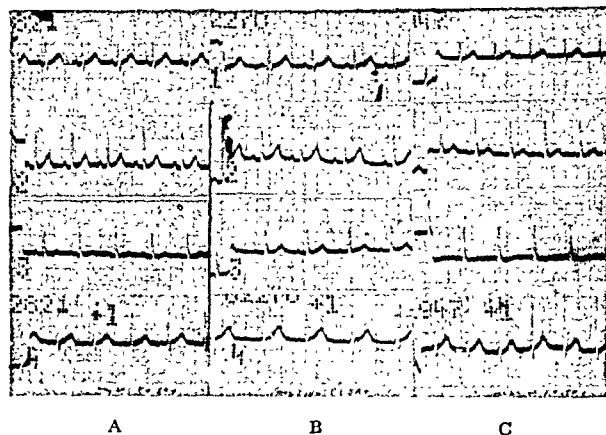


FIG. 5. A, record of May 20th; B, record of May 1st; C, record of April 22nd.

sixth, etc. In other words, there is an alternating variation in the height of the T wave which is considered to indicate a disturbance of myocardial function.

The next figures are serial records of New York Hospital patients with rheumatic fever. In Figure 5 the record on the right was obtained April 22nd from a patient at the beginning of an attack of acute rheumatic fever. The May record was obtained at a time when there was no fever but there was an increased sedimentation rate. It was a mild attack. This patient on April 22nd had a tachycardia with a rate of 100 and again it was a nodal tachycardia. The P wave shows as a notch just following QRS in two leads proving that this was a nodal tachycardia. The T wave was of average voltage. The bottom lead is the fourth lead, the precordial lead 4F. On May 1, there was a normal sinus rhythm. The rate was about 80 per minute and the T waves had a normal appearance in all four leads. However, the sedimentation rate was still increased at this time although fever was absent. You will notice the change in the appearance of the T wave. It has acquired more voltage. It is larger in amplitude than it was on April 22nd. Such changes are not infrequent and probably have some significance, in this case indicating a changed condition of the myocardium. A record was obtained on May 20th, a month after



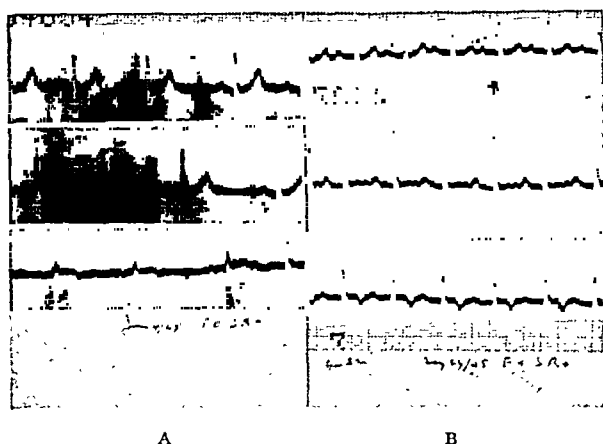


FIG. 6. A, record of June 4th; B, record of May 24th.

the first one. At that time there was tachycardia, the rate being 100 per minute. The auricular-ventricular sequence was normal and the ventricular complex was normal. There was no fever; the joint symptoms had subsided, but the sedimentation rate was still increased.

Figure 6 was obtained from another patient. This patient on May 24th had an apical systolic murmur, fever and an increased sedimentation rate. At that time, as seen in the record on the right the A-V conduction time was prolonged, P-R measuring 0.24 second. The QRS group was not abnormal but the T wave in lead II had a peculiar notched appearance which is often the forerunner of an inversion of the T wave. In this case, however, the next record, obtained on June 4th, at which time the fever had subsided although the sedimentation rate was still increased, showed a normal A-V conduction time. There was a sinus arrhythmia. The T wave, however, had increased considerably in voltage and the peculiarity of  $T_2$  was no longer present.  $T_3$  had an unusual appearance in the slight elevation of the S-T junction and the downward peak at the end of T. The last beat in lead III was an auricular premature beat.

Figure 7 shows two more records of this same individual. The one on the right was obtained on June 25th. There were intermediate records which I left out because

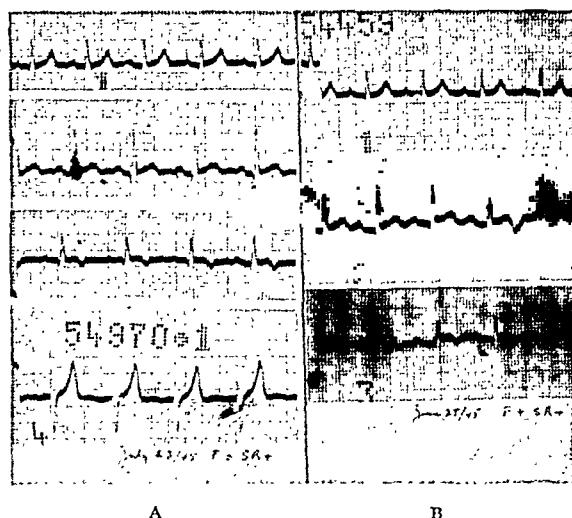


FIG. 7. The same case as Figure 6. A, record of July 23rd; B, record of June 25th.

they did not show any significant changes. At that time the patient had a reappearance of arthritis and fever, very mild arthritis and not much fever. The sedimentation rate remained increased. The auricular-ventricular conduction time was again prolonged to 0.24 second; the QRS group was the same. The S-T junction in lead III was elevated a full millimeter, which was not so before. In lead II also there was an elevation of 1 mm. which was not previously present. Besides the change in the S-T junction, the voltage of T in Figure 6 was much larger than in Figure 7. The change in voltage of T and in the elevation of the S-T junction indicated a change in the state of the myocardium. A record was obtained July 23rd at which time the patient was about ready to be sent home. Though he had no fever, the sedimentation rate was still increased. The S-T elevation, which was present in lead II had been considerably reduced and in lead III the S-T elevation had disappeared; the voltage of T had slightly increased. The fourth lead contributed nothing in this case.

Figure 8 is a third case. The first record at the right was made when the patient was ambulatory and did not demonstrate any acute rheumatic manifestations. It may

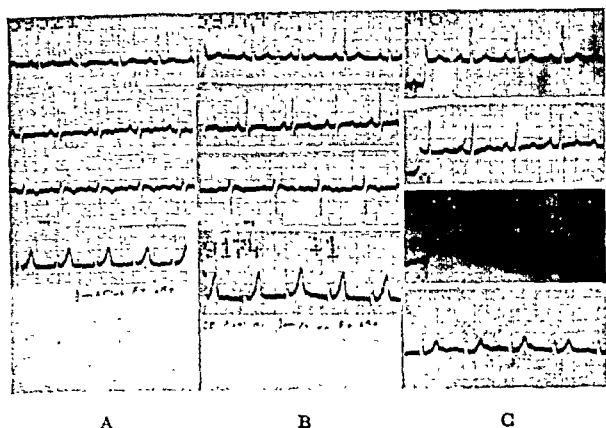


FIG. 8. A, record before acute attack; B, record of January 14th; C, record of January 25th.

serve as a control. Four leads are shown and there is nothing unusual about it except the left axis deviation. The patient had murmurs which led to a diagnosis of aortic stenosis and insufficiency with mitral insufficiency. He had a very large heart and was a man of about forty-five years of age. January 14th was a couple of days after the beginning of an acute rheumatic attack which did not make itself very evident in the joints but which was associated with definite fever and increased sedimentation rate. If we had only seen this record without having seen the previous one we might hesitate to say that that T wave was abnormal, but having seen the earlier record, I think it is proper to say that this is abnormal. The S-T segment in lead II is somewhat elevated, and the T wave does not have the normal type of curve concave upward toward an apex, which we see in lead I of this record and in lead II of the previous one. The large upward T wave in lead IV is also unusual. There is no change in the P-R conduction time. The tracing taken on January 25th, seen on the left while fever was still present and the sedimentation rate increased, showed abnormal T waves in lead II with inversion and perhaps a little coving of the S-T segment, an upward convexity. There was no change during this time in the murmurs that were

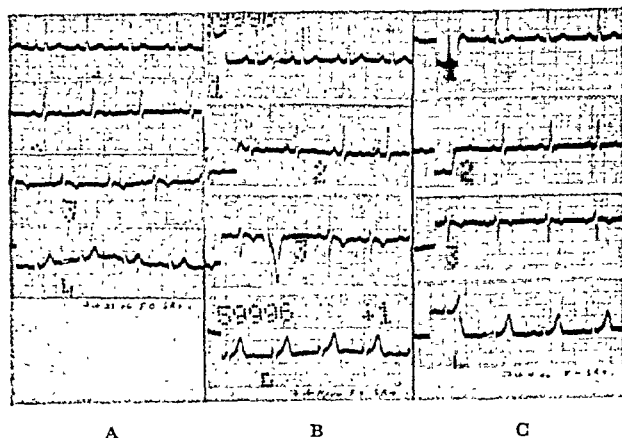


FIG. 9. The same case as Figure 8. A, record of February 23rd; B, record of February 11th; C, record of February 4th.

found over the precordium. They remained the same.

In Figure 9 the record on the right was obtained on February 4th, nine days later. The T wave in lead I is upward; the T wave in lead II has assumed a form which you might consider normal if you had not seen the earliest record. I think, however, it might be called normal. There is no significant abnormality in this record and the P-R interval is normal. There was no fever at this time and the sedimentation rate was increased. On February 11th, seven days later, fever had reappeared. The record shows a change in T<sub>2</sub>. It becomes diphasic. In lead III a ventricular premature beat makes its appearance. Twelve days later, on February 23rd, there is no fever. The sedimentation rate is still increased. The T wave of this record in lead II appears about as on February 11th.

In Figure 10 we see on the right the record of March 8th, two weeks later. During this time there had been no more fever and no more joint manifestations. The process was apparently subsiding but the sedimentation rate was still increased. The T wave in leads II and IV is returning somewhat more towards normal. Here is an example of how the diagnosis of activity of rheumatic fever may be aided by the electrocardiogram. There was nothing in this patient's clinical

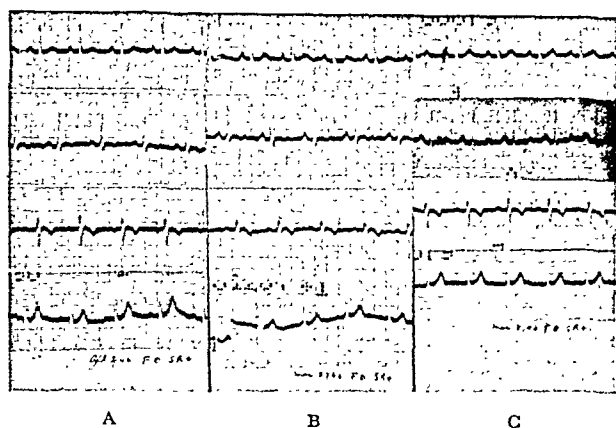


FIG. 10. The same case as Figures 8 and 9. A, record of April 3rd; B, record of March 27th; C, record of March 8th.

appearance between March 8th and April 3rd to indicate that his condition was not progressively improving. Yet this T wave, which was essentially normal on March 8th, has become definitely abnormal on March 27th and on April 3rd is still definitely abnormal. At this time the physicians were so impressed with the fact that the man had clinically recovered from his rheumatic fever that they sent him home with this progressing abnormality in the T wave. It seems to me that this was an indication of activity of the rheumatic process and that he should have been kept in the hospital until the T wave returned to normal or stopped showing progressive changes. These electrocardiographic changes are found with a frequency which has never been accurately determined because the frequency with which you find these things is going to depend upon how often you look for them.

There are only two series of cases in which daily records have been taken. Dr. Cohn took daily records of thirty-seven cases. Dr. Master and Dr. Jaffe took daily records of sixty-three cases. Dr. Cohn found 93 per cent, which is all but two of his cases, to have some form of abnormality of the electrocardiogram during the course of their illness. Master and Jaffe found 100 per cent of their cases to have some signifi-

cant change in the electrocardiogram. This includes arrhythmia, form changes and P-R changes. If you look for it daily, you will find electrocardiographic changes in practically 100 per cent of rheumatic patients. The percentage of findings are interesting in different series. They read as follows: 100, 100, 95, 94, 93, 92, 90, 94, 70, 67, 40, 22. In the last group, electrocardiographic changes were found in only 22 per cent of patients who had chorea, and they had only about three records from each patient in the course of a number of months. That is why they found only 22 per cent to show any abnormality. If they had taken more frequent records, I am sure that they would have found more frequent changes.

The relative frequency of P-R changes and T wave changes is of interest, but is found nowhere in the literature. The authors have not attempted to distinguish statistically between changes in P-R and changes in T waves. True, it is not very important, for the findings indicate activity of the disease in either case. But it may be a matter of more than academic interest whether the activity lies in the A-V conducting tissue or in the ventricular myocardium which produces the T wave. Master and Jaffe, who have the largest number of daily records of patients, found increased P-R time in 65 per cent, and in one-third of these the conduction disturbance went to the degree of dropped beats. They did not report any cases of complete heart block. Dr. Cohn in his thirty-seven cases found complete heart block in one case. He found bundle branch block in three cases. Master and Jaffe did not find it at all in their larger series. Therefore, it must be an infrequent happening. Master and Jaffe found abnormal S-T and T wave changes in 85 per cent of their cases. Cohn does not distinguish statistically between the two types of change. The

arrhythmias occur with a variable frequency in the different series, but I think that Cohn's findings on the arrhythmias are the best reported. In thirty-seven cases he found auricular premature beats ten times, not in ten cases but ten times; auricular fibrillation five times; auricular flutter once; auricular tachycardia five times. He found sino-auricular block once. He found A-V nodal premature contractions three times. He noticed A-V nodal rhythm five times. This does not give you the idea of the number of cases that developed these things but only the frequency of occurrence in the series of cases. He found prolonged P-R and heart block combined ten times. A-V rhythm is perhaps one of the most common types of arrhythmia that we encounter, if you exclude the dropped beats which are associated with the higher grades of heart block.

With less frequent records, a different picture is presented. Dr. May G. Wilson reports on fifty-four hospital cases with acute rheumatic fever. She found prolonged P-R or abnormal T wave or elevation of S-T or some other arrhythmia in 33 per cent. In these cases, records were taken about once a week. In 860 ambulatory patients whose records were taken occasionally, 22 per cent showed some sort of electrocardiographic abnormality. It is important to bear in mind that these electrocardiographic abnormalities occasionally may be found when the patient does not show any other evidence of rheumatic activity though, as I said before, the sedimentation rate is usually coincidentally affected. When electrocardiographic abnormality occurs without the sedimentation rate being affected, I would be inclined to attribute it to a fibrotic myocardial change rather than to an acute inflammatory reaction. In most patients, the disturbance of the record entirely disappears when the disease disappears and only a small percentage is found to have

any abnormality in the electrocardiogram after the acute phase of the disease. Right or left axis deviation of QRS affords an exception here which might be due to hypertrophy of one or the other ventricle of the heart.

#### DISCUSSION

DR. TARAN: It is commonly taught that there are three distinct types of disturbances in the electrocardiogram in acute heart disease; one refers to rhythm, one refers to muscle change, and the last refers to possible changes in the size of the heart, as ventricular strain. Are there any changes in the electrocardiogram that might be significant of disturbances in the functional integrity of the heart? For instance, in acute infarction one may find that the systolic period of the heart is increased. In hypocalcemia, in hypopotassium states, when there is a disturbance in the functional dynamics of the heart, there is also a disturbance in the sequence of events in the cardiac cycle. Can this disturbance of sequence of events be considered a criterion of an acute inflammatory process of the heart muscle itself?

DR. PARDEE: Yes, I think so, definitely. I always look upon the electrocardiogram as a record of a physiological function of the heart, one which is unrelated to all other functions except perhaps the chemistry of the heart muscle. That, after all, is the basic function which produces the electrical potential. In the course of disease there are physiological changes in the muscle, changes due to the inflammatory reaction which is present, to the edema, to the encroachment upon the muscle bundles by pressure, and I do not know what the Aschoff bodies do, but they probably represent chemical irritation of some sort. I think that all those things, any one of them, may change the electrocardiogram. It may change the S-T junction or the T wave, or

it may cause an arrhythmia of what I call the irritative type, the premature beat or a tachycardia, no matter where it occurs in the heart. Only when we have permanent structural changes do we get permanent electrocardiographic changes. That is why I think that all of these things should be looked at as being on the physiological level. They are due to changes which we can see only occasionally with a microscope.

Edema is the main change which we can see. Fever itself does not seem to cause this type of electrocardiographic change. I do not think that these patients with acute rheumatic fever are usually subject to disturbances in their calcium metabolism, so I question if that could be used as anything but an illustration of a type of abnormality that can change the electrocardiogram. I think the lesson from all this is that in following a patient with acute rheumatic fever it is advisable to take electrocardiographic records from time to time, especially approaching the time when you think it is all over and the patient is getting better. If you then find abnormalities in the T wave or in the conduction time, I think this is an indication that it is not over; I think that the percentage of cases that come through rheumatic fever with permanent electrocardiographic changes is very small, perhaps 1 or 2 per cent and that they have this because of fibrosis.

DR. GELLER: It was my impression as I saw those slides that some of those T waves showing changes in voltage also appeared peaked and symmetrical. The T's were definitely abnormal in that they were peaked and symmetrical rather than normal and asymmetrical.

DR. PARDEE: I think that that is a very interesting observation and perhaps one that I have not appreciated. I think that this may be a new feature of the abnormal T wave that we may recognize as being due to myocardial abnormality.

DR. GOERNER: In rheumatic fever do you ever see changes in the S-T and T waves in the precordial leads that are not evident in the other leads?

DR. PARDEE: Yes, I think you do. These records that are shown here happen to have normal precordial leads in each case, even when the limb leads are abnormal, but there are other cases in which the precordial leads are abnormal and the limb leads are normal. The frequency of that I could not tell you. It has never been studied to my knowledge. Although I know of one series of cases reported by Levy and Turner in which they studied precordial leads, yet they were concerned more with serial changes in the same patient. I do not think they reported on the number of precordial leads that were abnormal when the limb leads were normal. They were concerned with changes in precordial leads from one time to another. However, I am sure from what I know of the electrocardiogram that there must be many cases that will show an abnormality in the precordial lead and yet have normal limb leads.

DR. GOERNER: Would you consider a sharp inversion of the T wave in precordial leads in a thirteen-year old child significant?

DR. PARDEE: I would want to be sure that it was obtained at position four because the placement of the precordial electrode is one of the biggest stumbling blocks in electrocardiographic technic. If it was not placed near the sternum, if it was at the apex, the child being thirteen years old, I would think that an inverted T wave in such a patient would certainly mean an abnormality of the myocardium of some sort.

DR. GOERNER: Even as an isolated finding?

DR. PARDEE: Yes.

DR. WATTS: Then we are to infer from your answer to the last question that there are precordial leads with the T wave inversion that can be considered normal? In

other words, T wave inversion, possibly more to the right than to the left of the apex, can be considered within the limits of normal?

DR. PARDEE: Absolutely so in children. In adults, particularly in women of the hyposthenic type, leads from near the sternum, position II or even position III in children, may show an inverted T wave in individuals that are, I believe, normal. And in adults, in women of the hyposthenic type, a T<sub>3</sub> may be inverted.

DR. WATTS: And five and six?

DR. PARDEE: But not in four or five.

DR. WATTS: When you see a bundle branch block on the electrocardiogram of a patient whose past history is unfamiliar to you or when the patient denies all previous illness, do you interpret such a finding as myocardial injury and damage or can that be within the limits of normal?

DR. PARDEE: I would feel, if I saw a record with bundle branch block, that the patient's heart was abnormal, that is, it had some pathological change. I understand that Willius has advanced the idea that it may be a normal phenomenon. I cannot understand it as such.

DR. WATTS: In the army we often observed bundle branch block in apparently normal individuals, often times men who had previously been athletes and had had no sign of heart disease. It would always become a great problem as to whether that patient should be discharged from the army on that simple finding. As a matter of fact, the principle was followed that they were discharged, but it always used to bother me.

DR. TARAN: Is it not conceivable that those were congenital findings and did not interfere with the function of the heart, permitting these individuals to become athletes. From the functional standpoint, therefore, they may be considered as normal.

DR. PARDEE: That bundle branch block

may be a congenital anomaly in association with other congenital disease is well known, but the type of case referred to, I understood, had no other evidence of heart disease. As an isolated congenital anomaly, I am not acquainted with it. That may be Willius' contention. It is certainly obvious that people can have bundle branch block and have no apparent impairment of their cardiac reserve. Why should they? It makes very little difference to the heart function whether one ventricle goes off two or three-hundredths of a second after its normal time. So I can understand a very sharply localized disease affecting a bundle branch and not affecting much else of the myocardium, which might not cause the heart to be below normal in its functional capacity.

There are many such patients. The first time I heard of this was many years ago. I received an electrocardiogram from the West. A doctor had bought an electrocardiographic machine and had taken a trial record of his brother who was thirty-five years of age. It showed right bundle branch block. He sent it to me in consternation. What could he do about it? That has been cropping up ever since; a great deal of it was found in army work. All we know about it would lead us to believe that it is due to a small focus of disease.

DR. BATTRO: I have just published a paper on the precordial leads of children. We found that the inverted T wave in the precordial leads in normal children are different in form from the inverted T wave in abnormal cases. The ascending limb of the T wave in normal children is long and reaches or, in fact, rises above the iso-electric line, whereas in the abnormal heart it does not reach this point.

DR. PARDEE: Very interesting. I did not know that.

DR. BATTRO: And after ten years of age we never found a T wave inversion in the precordial leads IV, V or VI.

# Case Reports

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## Histoplasmosis

### *Report of Diagnosis from Biopsy of Cutaneous Nodules\**

WILLIAM A. THOMAS, M.D. and JAMES HERBERT MITCHELL, M.D.

CHICAGO, ILLINOIS

WORKING independently, Major Leishman in May, 1903, and Captain Donovan in July, 1903, identified and described the organism responsible for kala azar. Armed with this knowledge, Darling<sup>1</sup> of the U. S. Public Health Service in Panama, reasoned that there should exist in that region of the New World a disease which has such widespread distribution in the tropics of the Near and Far East. In 1905, while examining the lungs, liver, spleen and bone marrow of a Martinique negro, he encountered numerous tubercles, presumably miliary tuberculosis, in which no acid fast organisms could be demonstrated. By the use of other stains, he observed intense invasion of endothelial cells by small, round or ovoid bodies, about three microns in diameter, with refractile peripheries and non-homogeneous internal structures. It is to the credit of Darling that he did not accept these organisms as Leishman-Donovan bodies and that, failing to find with polychrome methylene blue-eosin stains the chromatin rods characterizing the latter, he concluded that he had discovered an hitherto unknown organism responsible for a fatal infection in a native of this hemisphere. He regarded the organism as protozoon in character, an opinion concurred in by Major Ronald Ross, and named it *Histoplasma capsulatum* and the disease histoplasmosis. In 1906, two additional cases reported in detail in 1908<sup>2</sup> were found.

During a period of three years, among 33,000 admissions to Ancon Hospital, no additional cases were encountered.

It was not until 1925 that a fourth case was observed when Riley and Watson<sup>3</sup> found the disease in a fifty-two-year old German-born female patient, who had not been outside of Minnesota for the last forty-four years. Generalized lymphadenopathy, splenomegaly and cirrhosis of the liver were present. With routine hematoxylin and eosin stains, the invading organisms were at first entirely overlooked. They were clearly revealed later with Weigert-Gram, Giemsa, Bensley's aniline, acid fuchsin and methyl green, and phosphotungstic acid—hematoxylin stains. Initially they were considered to be Leishman-Donovan bodies, but were later shown to be identical with Darling's *Histoplasma capsulatum*. Watson<sup>4</sup> published a detailed account of the histologic findings with special discussion of the origin of the phagocytic cells.

Because of its close resemblance to the Leishman-Donovan body, Darling, Ross and others considered *Histoplasma capsulatum* to be a protozoon. However, Rocha-Lima<sup>5</sup> as early as 1912, after studying Darling's material, believed that it was a yeast-like fungus, an opinion confirmed when De Monbreun<sup>6</sup> succeeded in growing the organism *in vitro* in a yeast-like form typical of fungus, with production of

\* From the Presbyterian Hospital, Chicago, Illinois.



FIG. 1. X-ray of lungs. A, April, 1943, slight increase of density at right base; B, four weeks later, generalized increase in lung markings. Diagnosis: x-ray, low grade inflammatory infection, possibly blastomycosis.

mycelia and spores. Conant,<sup>7</sup> in his comprehensive study of its growth characteristics, classified it in the Moniliaceae group of Fungi imperfecti. The yeast-like form alone is pathogenic to humans, has never been recovered outside of the human body, and on artificial media exhibits typical spinate or barbed forms (Fig. 3A.) as contrasted with the mycelial type which has been recovered from dogs, possibly rats and other rodents. Neither form has been recovered outside of mammalian bodies. By appropriate cultural methods, either form can be converted to the other.

Since the fungus does not appear to exist freely in nature, nothing is known of the portal of entry or method of infection, but as the entire gastrointestinal tract, respiratory system and skin are commonly involved, they presumably constitute the most frequent sites of infection. The disease is apparently not very contagious as there are no published reports on consanguinity, contact, or exposure resulting in infection. Demonstration of the fungus character of the organism, as contrasted with the protozoon nature of the Leishman-Donovan body, detracts from the value of Patton's<sup>8</sup> impor-

tant observation that the latter, in all stages of development, may be found in infected bed-bugs. Furthermore, in contrast to histoplasmosis, it is reported that in kala-azar the cutaneous and systemic forms of the

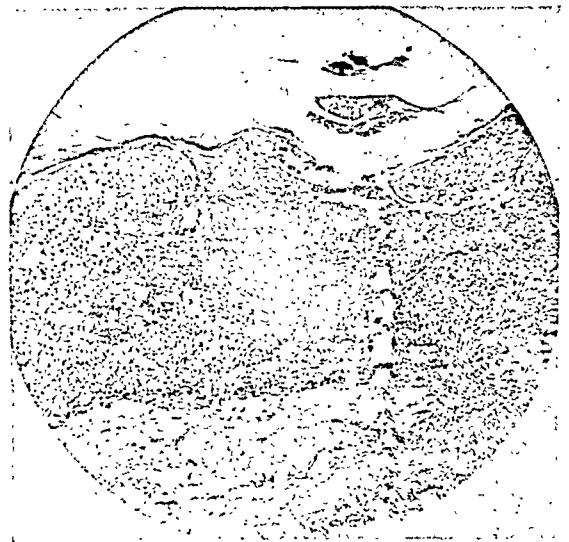


FIG. 2. Low power section of cutaneous nodule obtained by biopsy.

disease do not manifest themselves in the same individual, at any rate not at the same time.

Since there have recently been numerous excellent and detailed accounts of the manifestations of histoplasmosis, reviewing



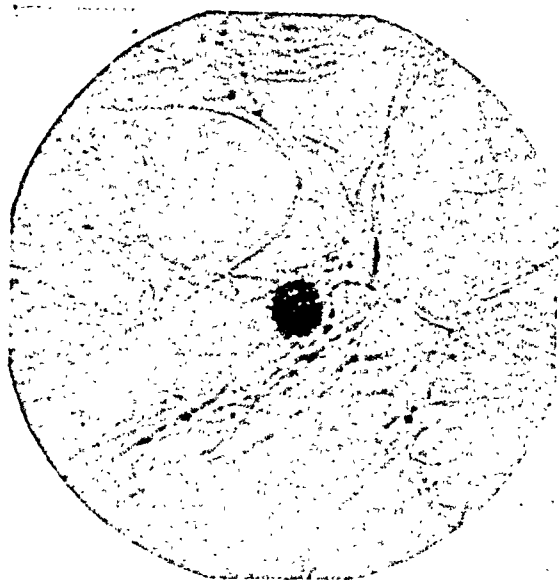


FIG. 3. A, growth of *Histoplasma capsulatum* from blood culture on blood agar plate at room temperature, showing characteristic spinate form of yeast form pathogenic to man.

present knowledge of sex incidence, age, occupation, methods of diagnosis, incidence and distribution, as well as full descriptions of the disease in the human body, no attempt will be made to recapitulate these facts. Broders et al.<sup>9</sup> published a review of the literature with a case report of vegetative endocarditis of this origin. Parsons and Zарафонетис<sup>10</sup> have more recently presented a complete bibliography and extensive discussion, including summaries of seventy-one published cases with a detailed description of ten of these.

The increased number of cases reported, especially since 1936, is due in all probability to more general recognition of the disease. Clinically this has been accomplished by more frequent sternal or tibial punctures, blood smears, biopsy, and in particular by realization of the slow growth of the organism both at incubator and room temperatures (thus avoiding the practice of too rapid discarding of cultures, since growth may appear as late as twelve or even eighteen days). Pathologists, bacteriologists and parasitologists have also become more familiar with the material obtained by culture or at postmortem and consequently



FIG. 3. B, growth on Sabouraud's medium at room temperature.

have recognized the organism more frequently. A diagnostic cutaneous test by intradermal injection of the filtrate of a broth culture of the organism has also been reported.<sup>11</sup>

Histoplasmosis until recently has been considered an invariably fatal disease. However, there have been recent reports of healed, calcified lesions, ostensibly tuberculosis, which after careful examination were considered to be healed histoplasmosis. Parsons and Zарафанетис<sup>10</sup> described apparent recovery from local, ulcerated lesions following x-ray therapy, and in cases in which the infection was limited to lymph nodes, cure by the use of antimony preparations and by diamidine.

#### CASE REPORT

A seventy-two year old woman, who had been under our medical care for many years,

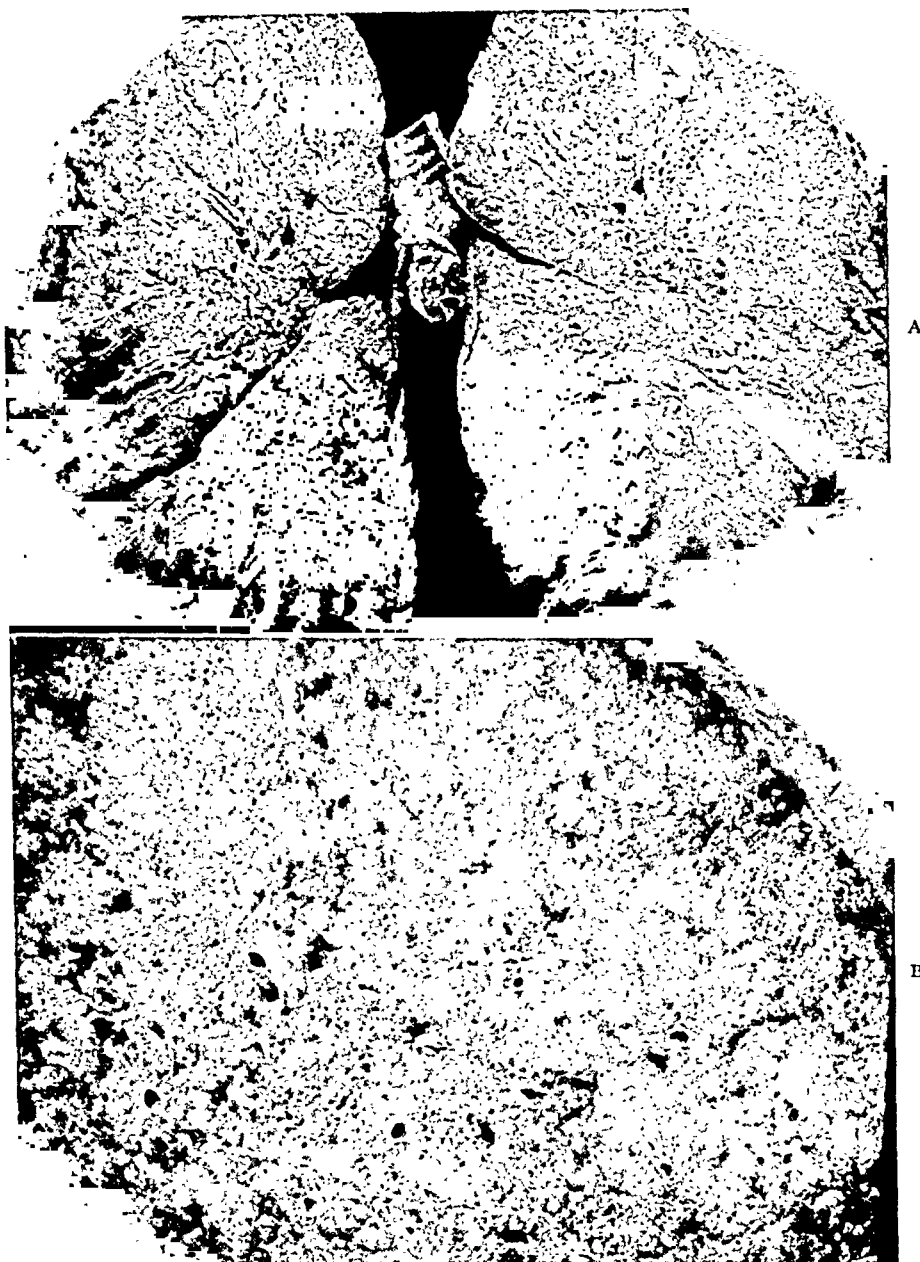


FIG. 4. A, gross section of lungs; B, fibrocascous involvement more generalized and uniform than in pulmonary or miliary tuberculosis.  $\times 73$ .

came to the office January 4, 1943, for a routine, semi-annual examination before going to Florida. She had always been in excellent health, was an alert, active person taking part in many civic and community affairs, and except for a known diverticulum of the esophagus, had had no illness or abnormality. Thorough questioning and examination at that time revealed no indication of disease.

On her return in April, 1943, she presented a striking picture of advanced Addison's disease; appearing thin, with marked pigmentation of the entire body, especially noticeable on the exposed portions, and was obviously weak

and desperately ill. Her symptoms were anorexia, nausea and vomiting, diarrhea, weakness and loss of ten pounds in weight. History revealed that she and her husband had what was presumed to be the then prevalent virus enterocolitis (intestinal influenza) from which he had promptly recovered. She, however, had a chill at the onset, with fever lasting for five days, after which a persistent, non-productive cough developed. In spite of medication and a carefully maintained colitis-type diet, all symptoms persisted and she was sent immediately to the Presbyterian Hospital. Remembering that her sister had died two years previously of peri-



FIG. 5. Liver, round and ovoid bodies both intracellular and extracellular.

arteritis nodosa, after a prolonged illness with fever of obscure origin and symptoms in many respects similar to those of the patient, this diagnosis was primarily considered. On admission she had fever ranging from 100°F. to 103°F., which persisted until death. Examination re-

examination of numerous stools and serological tests for undulant fever and typhoid, as well as the Kahn test, were normal. In spite of her cough, no sputum was ever obtained.

She was allowed to go home, where she was seen frequently. But as her condition became progressively unfavorable, she returned to the Presbyterian Hospital one month later, May 18th, having lost an additional twelve pounds, with persistence of cough, anorexia and nausea. Diarrhea had ceased. There were râles at the base of each lung posteriorly. X-ray (Fig. 1B) of her chest showed marked increase in density in both lungs as compared with the film taken one month previously, the markings being suggestive of a low-grade infection, possibly blastomycosis. Blood pressure was approximately as before, 158/86. At this time she had in the web of the right hand between the thumb and first finger, a hard, umbilicated nodule or papule which was very tender and painful and in spite of her other discomforts, she complained bitterly about it and maintained that it was very important. Four days after admission, her nurse reported a

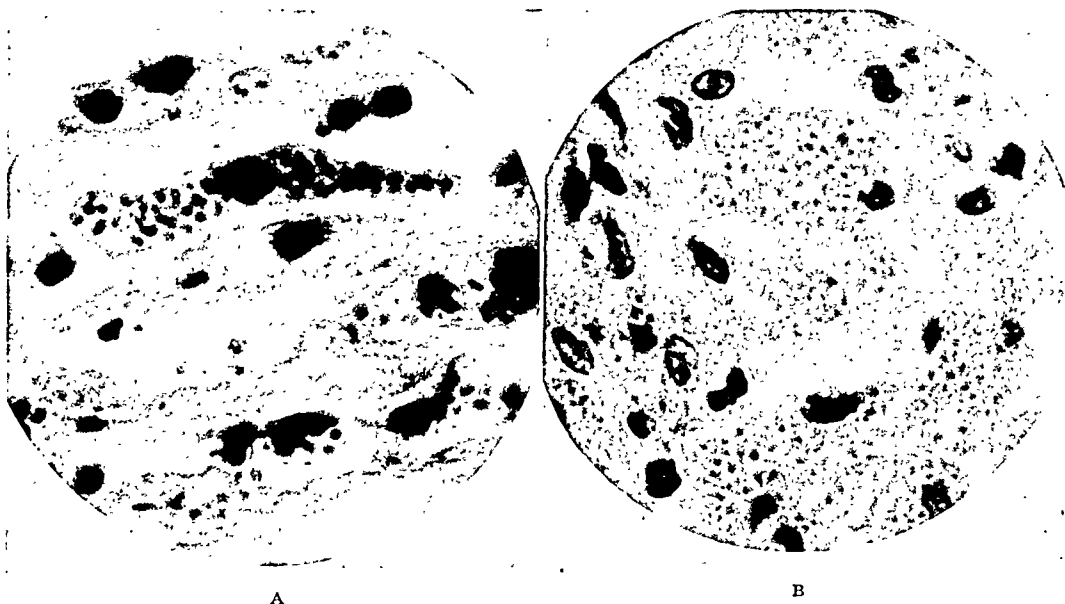


FIG. 6. Adrenal cortex; A, high power; B, oil immersion, invasion of cells and extensive caseation necrosis of tissue.

vealed a tender mass in the right upper quadrant, a gallbladder filled with stones and failing to concentrate dye, normal gastric acidity, blood pressure 150/80, confirmation of esophageal diverticulum, white blood cell count 4,500 with normal differential, and normal chest x-ray. (Fig. 1A.) No amebae were found in

crop of similar lesions about her neck and shoulders posteriorly and on the following day a large number, perhaps fifty, appeared rather generally distributed over the body. They were very painful, especially with pressure, so that she could not be comfortable in any position. Sections were obtained by biopsy (Fig. 2)

(J. H. M.). The pathological report showed numerous fungus-like organisms were present, diagnosis blastomycosis. Not satisfied with this, a second biopsy was performed and the material obtained was studied by examination of stained, macerated tissue on slides, and by sections, each method revealing an organism identified as *Histoplasma capsulatum*. Culture of the fresh material later grew an identical body. The day on which the second biopsy was performed, positive blood cultures appeared on Sabouraud's medium after nine days' growth at room temperature and the characteristic yeastlike form with spinate configuration (Fig. 3) confirmed the tissue biopsy findings, as did subsequent growth from this latter source. No specific (antimony) therapy was instituted and death occurred June 20th.

Complete autopsy confirmed the antemortem diagnosis of histoplasmosis. The entire reticulo-endothelial system was involved. The anatomic diagnosis follows: Histoplasmosis of lungs, liver, spleen, kidneys, adrenal glands, trachea, thymic fat, skin; also tracheobronchial, parapancreatic and mesenteric lymph nodes; extensive fibroid mycosis of the lungs; generalized embolic papular and ulceropapular mycosis of the skin; extensive coagulation necrosis of the adrenal glands; moderate brown pigmentation of the body, especially the exposed portions of the upper extremities; mycotic focal glomerulonephritis was evident with minute focal mycotic granulomas of the liver and spleen and focal necrosis of the liver, as well as subacute hyperplasia of the spleen. The other findings were not relevant.

#### COMMENT

Of particular interest, considering the striking resemblance to Addison's disease, is the extensive involvement of the adrenal glands and the presence of extensive coagulation necrosis. No normal adrenal cortical tissue remained and where isolated groups of cortical cells could be identified, they appeared to be undergoing coagulation or hyalin necrosis. (Fig. VI A and B.) Furthermore, despite the clinical picture, as well as the gross and microscopic evidence of almost total adrenal cortical destruction, the

blood pressure remained elevated throughout (148/74) to within thirty-six hours of death.

In view of the extensive and generalized embolic cutaneous papular lesions in this patient, it is of interest to record that Darling, in Case 3, notes "the presence of cutaneous papules."

#### SUMMARY

A case on first impression presenting a syndrome resembling acute adrenal cortical insufficiency, and later that of a generalized fungous infection presumably blastomycosis, was demonstrated antemortem by material obtained from biopsy to be one of histoplasmosis.

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# Congestive Heart Failure Arising from Uncontrolled Auricular Fibrillation in the Otherwise Normal Heart

## Follow-up Notes on a Previously Reported Case\*

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**T**HAT auricular fibrillation may develop in an otherwise normal heart and without any discoverable cause is now a generally accepted fact. However, that prolonged overwork resulting from uncontrolled auricular fibrillation may of itself cause congestive failure in a heart free of organic disease is less generally recognized. The following case, which has been the subject of a previous report,<sup>1</sup> is now presented with additional notes extending over a period of eleven years.

### CASE REPORTS

**CASE I.** A woman aged forty-three years, from whose history there was excluded rheumatic, hypertensive, thyrotoxic or any other heart disease, suddenly developed auricular fibrillation followed three months later by severe congestive failure. The extent of the cardiac enlargement and pulmonary congestion is shown in Fig. 1.

After one week of bed rest and digitalization, normal rhythm was restored on June 18, 1935, by means of quinidine sulphate. Small maintenance doses of quinidine were continued for two days. All medication was then stopped and from July 20, 1935, to the day of the last examination, July 17, 1946, no treatment was administered.

During this period of more than eleven years the patient has remained in perfect health and has carried on an exceptionally active social and

economic life. Frequent physical, radiological and electrocardiographic examinations have failed to disclose any significant deviations from the normal. Figures 2, 3, 4, and 5 show the chest films and electrocardiograms recorded respectively in 1941 and at the last observation in 1946.

This case clearly demonstrates that severe congestive failure of a normal heart may be brought about by overwork resulting from uncontrolled auricular fibrillation. It also shows that in this type of case a complete and apparently permanent cure may be effected through the restoration of normal rhythm.

At the time of the first communication in 1937, the only similar case found in the literature was that of Parkinson and Campbell.<sup>2</sup> Since then two others have been reported, one by Levine and Beeson<sup>3</sup> and one by Trotter and Eden.<sup>4</sup> In the latter instance the arrhythmia was abolished by total thyroidectomy. The patient had been under observation over a period of eight years, and although the rate was controlled with digitalis therapy, the heart continued to enlarge and several episodes of congestive failure occurred. Following total thyroidectomy, regular sinus rhythm returned and the heart became normal in size. At no time before or after the operation were signs of thyrotoxicosis demonstrated and the thyroid gland was entirely normal macroscopically

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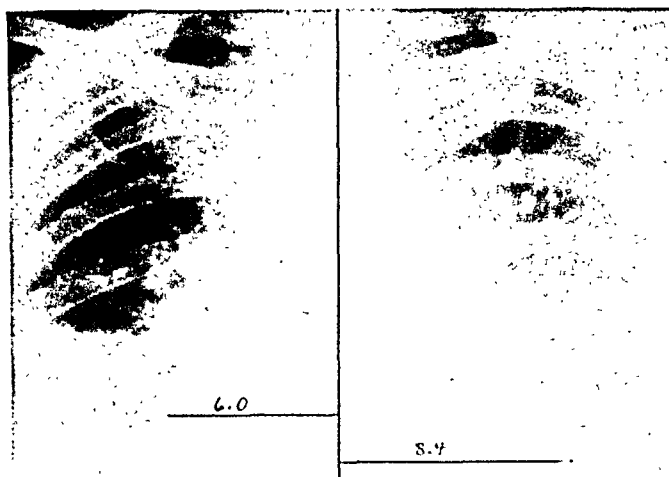


FIG. 1. Film taken June 8, 1935, showing passive congestion and fluid in pleural cavities. The transverse diameter of the cardiac shadow measures 14.4 cm.

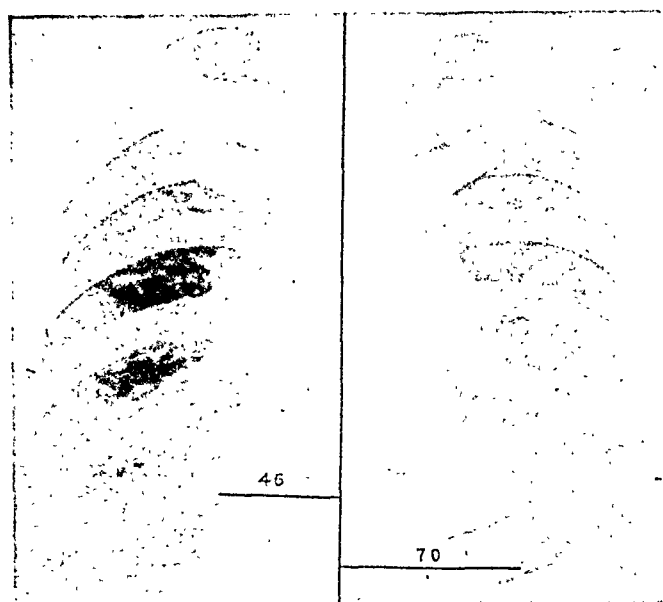


FIG. 2. Film taken September 2, 1941, showing no passive congestion and heart normal in size, shape and position. The transverse diameter of the cardiac shadow now measures 11.6 cm.

and microscopically. Presumably total thyroidectomy rather than quinidine therapy was elected in this case because of the prolonged history of auricular fibrillation and repeated attacks of congestive failure. However, Parkinson and Campbell's case which was analogous in duration and repeated episodes of failure responded equally well to quinidine therapy.

In the cases cited above the pathological processes induced by auricular fibrillation

appear to have been completely reversed by measures which controlled the cardiac rate and permanently abolished the arrhythmia. However, in similar instances if digitalis alone is used and no effort is made to restore normal rhythm, the continued heart strain and consequent cardiac enlargement may result in chronic and eventually fatal myocardial insufficiency.

Such a case has been reported by Gossage and Hicks.<sup>5</sup> A man aged twenty-three years



FIG. 3. Electrocardiogram taken September 2, 1941, showing normal tracing. Ventricular rate, 65.

during a coughing spell developed auricular fibrillation. A few hours after onset examination revealed the heart not enlarged and otherwise normal except for the arrhythmia. Although the rate was controlled by digitalis therapy, frequent examinations indicated gradual cardiac enlargement and one year after the onset of auricular fibrillation the apex beat was found to be in the sixth interspace, two inches external to the nipple line. Gross peripheral edema never developed but at varied intervals there were spells of precordial pain, palpitation and dyspnea. One and one-half years after the onset, while running across the road after a friend, the patient fell dead.

Autopsy revealed a large heart (600 Gm.) with completely normal arteries and valves. Numerous sections taken from various parts of cardiac tissues failed to reveal any abnormalities. The muscle fibers looked healthy, there were no collections of leukocytes and no increase of fibrous tissue.

It is possible that many similar cases remain unrecognized even at autopsy, due to complications which develop after a prolonged period of fibrillation and failure. The following case is an illustration.

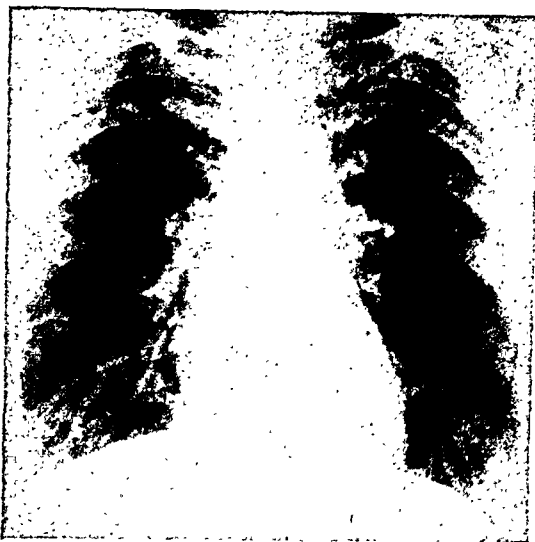
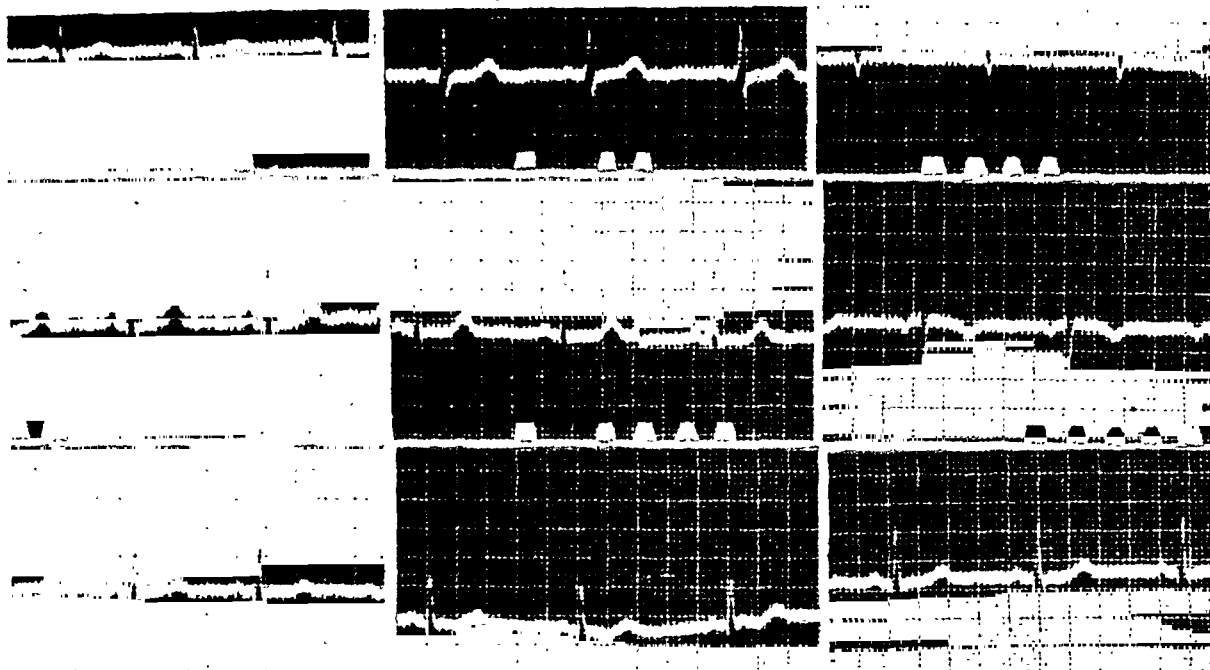


FIG. 4. Film taken July 17, 1946, showing no passive congestion and heart normal in size, shape and position.

CASE II. A man, aged forty-seven years, was first seen in April, 1936. His complaints were palpitation of some four years' duration, numbness of the extremities and dizzy spells. Examination disclosed a heart of normal size, a totally irregular rhythm and electrocardiographic evidence of auricular fibrillation. The blood pressure readings, the basal metabolic rate, and the blood and urine were essentially normal. During the ensuing years the heart remained in persistent auricular fibrillation and the rate was only poorly controlled by digitalization. After several episodes of congestive failure the patient died January 1, 1940 from pulmonary embolism.

During the final months of life he had suffered numerous embolic accidents involving the lungs, the brain, the extremities, and perhaps also a small branch of the left coronary artery. At autopsy the heart was found greatly enlarged (760 Gm.) The valves were normal. The coronary ostia were freely patent and serial sections of the coronary arteries showed only a slight degree of arteriosclerotic thickening. No areas of significant narrowing or complete occlusion were found. The myocardium was normal macroscopically and microscopically with the exception of a small area of thinning near the apex. This may have been the result of an occlusion (embolic?) of a small branch of the left coronary artery although no direct evidence of such an occlusion was found in any of the numerous sections studied. Other embolic lesions were



Standard Leads  
I, II, III

Unipolar Precordial Leads  
V<sub>2</sub>, V<sub>4</sub>, V<sub>6</sub>

Unipolar Limb Leads  
AVL, AVR, AVF

FIG. 5.

found in the left kidney, both posterior tibial arteries (canalized thrombotic emboli), the brain (in the region of the right internal capsule), and the lungs (bilateral pulmonary embolism). The multiple emboli undoubtedly originated from mural thrombi which were present in the left atrium and both ventricles. With the exception of an infarct in the left kidney no renal lesions were found. No arteriolar thickening was present to justify the assumption of hypertensive disease as an explanation for the extreme cardiac enlargement or for the onset of auricular fibrillation. The thyroid showed slight interstitial fibrosis, but no hyperplasia or lymphocytic collections were present.

This case illustrates the difficulties attending the attempt to determine the underlying etiological factors in a cardiopathy of this nature. Certainly at the time when auricular fibrillation was first noted none of the known causes usually responsible for such an arrhythmia could be demonstrated, and none could be definitely established at autopsy. It is not improbable that the arrhythmia was of itself the prime factor.

#### SUMMARY AND CONCLUSION

Follow-up notes extending over a period of eleven years are presented on a previously reported case. These observations together with others cited from the literature offer convincing evidence that overwork from uncontrolled auricular fibrillation may of itself produce cardiac enlargement and congestive failure in a heart otherwise free of organic disease. The importance of recognizing the functional nature of the arrhythmia in such cases and of establishing normal rhythm is pointed out.

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# Book Review

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**Biochemistry of Cancer.** By Jesse P. Greenstein, Head Biochemist, National Cancer Institute, National Institute of Health, United States Public Health Service. Pp. viii + 389, with 39 figures and 104 tables. New York, 1947. Academic Press, Inc. Price \$7.80.

The author has in this volume made available a comprehensive and authoritative summary and analysis of the contributions of the biochemical approach to the cancer problem. The appearance of the work is well timed, coinciding with the large-scale effort toward better understanding and control of the cancer problem now being organized. The present volume should help in orientation of that effort by facilitating evaluation of the biochemical studies in this field.

Following a brief introduction to the oncological sciences and a consideration of the general phenomena and taxonomy of cancer, the author considers the induction of tumors, attempts at control of tumor induction and growth, and the properties of tumors. The induction of tumors is discussed under the headings extrinsic factors (carcinogens) and intrinsic factors (sex hormones, mammary tumor inciter for mice, viruses). Attempts to control induction and growth of tumors are divided according to methods classifiable under nutrition, endocrinology and chemotherapy. The chemistry of tumors, a subject with which the author has been especially identified, and the chemistry of the tumor-bearing host comprise the main chapters of

the section dealing with the properties of tumors. A frank and objective appraisal of the present status of experimental and clinical cancer research concludes the text.

Thirty-nine figures and 104 tables are interspersed throughout the book. Each chapter is followed by a list of selected references. An author and subject index complete the work.

Dr. Greenstein has summarized an impressive amount of data dealing with the biochemistry of cancer and the cancer-bearing subject, particularly in connection with experimental animal tumors and in such fields as carcinogenic agents, mammary tumorogenesis in mice, and comparative enzyme studies in normal and neoplastic tissues. Even more impressive, however, is the amount of properly orientated investigation which, as the author makes clear, is still needed, particularly in the biochemistry of human cancer. It is evident that what has been accomplished is merely an indication of the potentialities of the biochemical approach to the problem of cancer.

Dr. Greenstein remarks that "cancer research at the present time appears to be conducted along two diverging streams, one experimental and the other clinical, and neither is very much aware of what the other is doing." The present volume should prove an important step forward in correcting this situation.

A. B. G.

## Editorial

### The Thymus and Myasthenia Gravis

SIR Astley Cooper was the real forerunner of a host of investigators who have endeavored without success to demonstrate some active principle or hormone in the thymus. The classical methods of endocrine research designed to produce deficiency symptoms upon removal and evidences of positive effect on administration or surgical transplant have been without results capable of repetition. The outstanding fact about this gland which stimulates interest is that it can be removed from the human subject in its entirety without endangering normal function in any demonstrable manner. There is much clinical evidence to suggest that the thymus has some as yet unknown endocrine function. The gland hypertrophies in the presence of hyperthyroidism, adrenal cortical hypofunction and gonadal hypofunction both in the male and female.

Abnormalities in the thymus are seen with great frequency in myasthenia gravis. Many endocrinological processes have a very definite influence on the course of this disease. The development of pregnancy often leads to a remission of symptoms while many women with myasthenia gravis become worse just before the onset of their menstrual flow. The relationship between myasthenia gravis and disease of the thyroid gland is well known but little understood.

Extirpation of all thymic tissue in patients with myasthenia gravis seemed to be

justified for trial as a therapeutic procedure and study of these patients after operation offered hope of obtaining clues as to the function of this gland which has for so long been an enigma. In about 15 per cent of the subjects the therapeutic results have been dramatic and by the use of modern physiological technics concrete evidence has been obtained of a reversion of neuromuscular function to normal. Further study of the clinical course of these patients and physiological studies with normal thymic tissue and with the material removed at operation are promising means for further elucidation of this intriguing problem.

Over 200 patients have now been treated by thymectomy. Many observers have been discouraged by the relative paucity of dramatic results; however, search for further clues as to why some patients are benefited and others are not should lead us not only to a better understanding of the disease but also of the normal processes of neuromuscular function and the various factors influencing it. In summarizing the results thus far from thymectomy, it may be said that those patients operated upon at an early stage of the disease are most likely to improve and that in general strength returns in the trunk and limb muscles more promptly and completely than in those muscles innervated by the cranial nerves. The remission after thymectomy does not depend on the presence of a discrete

tumor of the thymus for one of the most striking cures with complete freedom of symptoms for six years after operation was obtained in a patient with a moderately large, hyperplastic gland.

However, closer study of those patients with a thymoma is indicated. All of the tumors studied in Baltimore have shown varying amounts of neoplastic tissue derived from the epithelial cells of the thymic reticulum in addition to lymphocytic hyperplasia. Very frequently these tumors are not demonstrated by careful radiological examination although they may have reached a rather large size. The rapid increase in the severity of the myasthenia which often occurs in the presence of a thymic tumor is one of the striking observations, suggesting that this gland produces a substance which under certain circumstances interferes with normal function at the neuromuscular junction.

One of the characteristic features of the clinical course of patients with myasthenia gravis before the introduction of neostigmine therapy was the frequency of spontaneous complete remissions. The belief of some observers is that since the introduction of this therapeutic agent the incidence of these spontaneous remissions has diminished. There are still many cases in which the severity of the symptoms fluctuates but complete remissions lasting for any length of time are most unusual once neostigmine therapy has been introduced.

There is likewise suggestive evidence that the likelihood of remission following thymectomy is less if the patient has been on neostigmine treatment for more than a short period of time. As an example, one may consider the course of two male patients of the same age who had the disease for a comparable length of time and from each of whom a thymoma of approximately

the same size and cellular composition was removed. One man took neostigmine in large amounts for over two years preoperatively, while the other received antisyphilitic treatment because the thymoma was considered to be an aneurysm and the correct diagnosis was not made until the day before operation. The untreated patient promptly recovered following thymectomy while the other had no relief of symptoms and died a year later.

The mortality associated with the operation is low if the postoperative care is in the hands of clinicians experienced in the handling of patients with this disease. The chance for recovery from myasthenia gravis after operation is greater if thymectomy is performed early in the course of the disease; indeed, it may be equal or better than the chance that the disease will remain so mild that it can be easily controlled by the therapeutic methods available and will allow the patient to lead a relatively normal life. Serious consideration must be given by those clinics having facilities to handle patients with this disease to the view that thymectomy may be the treatment of choice if done as soon as the diagnosis of myasthenia gravis is made. Further results in a series of cases operated upon at this stage, regardless of the severity of the symptoms, may also clarify the relationship of the thymus to this disease and furnish clues to the normal physiological function of this mysterious organ.

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## Antibacterial Precipitating Antibodies in Group A Hemolytic Streptococcus Sore Throat\*

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INTEREST in hemolytic streptococcal disease has been enhanced during the last decade as the result of the presentation of evidence<sup>1</sup> that rheumatic fever is a sequel to infection by these organisms and by the appearance of new information<sup>2</sup> in regard to the nature of the infectious agent. Hemolytic streptococcal infections in man, particularly of the respiratory tract, are caused by members of a single serological group designated by the letter "A," the members of which may be segregated into types by agglutination or precipitation technics.<sup>2</sup>

Strains of Group A elaborate a number of filterable substances such as the erythrogenic toxin, hemolysin and the serum protease activator usually known as fibrinolysin. A neutralizing antibody for each of these often appears during convalescence in the serum of human beings who have been infected by Group A streptococci. Extensive studies have been made of these antibodies with special reference to the rheumatic state as well as glomerulonephritis.<sup>3-8</sup>

Antibacterial antibodies have attracted less attention and have not been studied in comparable detail. Various antigens and technics have been used for the purpose of

detecting immune substances in human sera capable of reacting with streptococcal cells or certain of their constituents.

Precipitin tests have been made using streptococcal protein, soluble at neutrality or in alkaline solutions (nucleoprotein)<sup>6,9-12</sup> protein soluble in acid, sometimes purified by precipitation with alcohol ("M" extracts with or without "C" carbohydrate,<sup>13-20</sup> purified "C" carbohydrate<sup>6,11</sup>) or extracts of the whole ground organism.<sup>12</sup> Earlier investigators studied the agglutination of hemolytic streptococci by human sera in an attempt to establish the etiology of certain disorders such as scarlet fever.<sup>22</sup> More recently others have described the presence of agglutinating antibodies in several human disease states and during convalescence from hemolytic streptococcal infection.<sup>16,18,20,23-26</sup>

Antibacterial antistreptococcal antibodies have been detected less frequently by animal protection tests<sup>27</sup> or by techniques involving the inhibition of growth of the living organism by whole blood containing phagocytes.<sup>28</sup>

Many of the studies mentioned above were carried out in groups of patients suffering from rheumatoid arthritis. Precipi-

\* From the Department of Medicine, Stanford University School of Medicine, San Francisco, California. This investigation was conducted under the auspices of the Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, Office of the Surgeon General, U. S. Army, Washington D. C. Dr. Paul J. Boisvert and Dr. Wesley W. Spink assisted in the clinical phase of the study.

tating or agglutinating antibodies were invariably discovered in the sera of a high percentage of such individuals, regardless of the nature of the extract or whole organisms used as an antigen in the test. The significance of these observations has never been determined. The presence of such antibodies may be an example of non-specific production of immune substances similar to the Well-Felix reaction, or it may indicate an intimate relationship between the disease and some variety of streptococcus. Further discussion of this problem will not be attempted in this paper.

As information in regard to the antigenic structure of the hemolytic streptococcus has accumulated, attempts have been made to demonstrate the presence or development of antibodies reacting with specific fractions. Most important are the studies of Coburn and Pauli<sup>18</sup> and Swift and Hodge,<sup>14</sup> who observed precipitating antibodies against purified acid extracts of Group A streptococci in streptococcal disease and rheumatic fever. These investigators have stated that there was a delayed development of such antibodies when a hemolytic streptococcal respiratory infection was followed by the appearance of some manifestation of the rheumatic state. In both instances it was originally believed that the antibody under study was reacting with the type specific "M" protein in the extract, but it has since become apparent that this was not usually the case,<sup>20,29</sup> since extracts from streptococci of a single type will induce precipitation with the sera of patients who are convalescing from an infection caused by organisms of several types. Similar non-type specificity has also been demonstrated for agglutinating antibodies.<sup>20,26</sup>

A systematic study of the development of antibacterial antibodies in a large number of human beings infected by Group A

hemolytic streptococci has rarely been undertaken.<sup>5</sup> A homogenous, closely controlled group has never been investigated under circumstances permitting the correlation of the antibody phenomena with the natural history of streptococcal respiratory disease.

It is the purpose of this paper to characterize certain antigens derived from Group A hemolytic streptococci and to describe the results of their use in precipitin tests in a large number of young adults who had suffered from infection by hemolytic streptococci.

#### MATERIALS AND METHODS

*The Precipitin Test. Organisms:* The hemolytic streptococci used in the preparation of precipitating antigens were isolated from the respiratory tract of infected human beings and grouped and typed by the serological methods of Lancefield.<sup>\*30,31</sup> The strains were in the matt phase when the extracts were prepared, and they yielded large amounts of the acid-soluble type-specific "M" substance.

*Antigens:* The technics used in the preparation of the antigens for the precipitin test will be described in another section.

*The Test:* The precipitin tests were carried out in a manner similar to that described for typing hemolytic streptococci.<sup>31</sup> The serum to be studied was drawn into sterile, thin-walled capillary tubes of 1.0 to 1.5 mm. in diameter followed by a similar amount of the sterile antigen solution. Great care must be exercised to obtain serum from under the fat layer if possible and to be certain that the serum and antigen are in contact without an intervening air bubble. It is essential that a saline con-

\* Group specific sera were prepared by the Lederle Laboratories and type specific sera by Squibb & Co. These sera were also used during other phases of the study for the detection and quantitative estimation of "M" protein and "C" carbohydrate.

trol be run with each serum. After filling, the small tubes were placed in plasticine in racks with the serum above the antigen solution.

The racks of tubes were incubated for twenty-four hours circa 36°C. and placed in the cold room for one week. The temperature was maintained circa 2°C. During the prolonged period of refrigeration a precipitate formed if the antibody was present and settled to the bottom of each tube where it could be easily seen and described. Saline controls were rarely positive. The results were recorded as follows: Negative—no, or very small amounts of precipitate; positive—definite precipitate, usually forming a column in the tube 0.5 mm. or more in height. This technic, which required small amounts of serum and extract, was very satisfactory and the results were entirely reproducible.

#### CLINICAL MATERIAL

The human sera used in the immunological studies to be described in this paper were collected during an intensive study of the natural history of Group A hemolytic streptococcal sore throats in young men. The nature of the group and the clinical and bacteriological information obtained have been fully described in a series of reports.<sup>1,32-37</sup> Clinical, clinicopathological and immunological data were available for 335 cases of streptococcal infection selected on clinical and bacteriological grounds. Definite infection was established in approximately 80 per cent of the patients by the development of a significant increase of the antistreptolysin titer during convalescence. Many of the other patients undoubtedly were, but cannot be proved to have been, infected. Some of these were examples of a non-streptococcal respiratory disease which occurred in an individual who was previously a Group A hemolytic streptococcal pharyngeal carrier.

#### CHARACTERIZATION OF THE ANTIGENS

Two antigens extracted from Group A hemolytic streptococcus cells were used in this study. They will be briefly characterized.

*The "X" Antigen.* Previous investigators have demonstrated that acid extracts of Group A hemolytic streptococcal cells contain a substance that will form precipitate with an antibody; this develops in the serum of human beings convalescent from an infection from these organisms and also in certain other pathological states. It was originally believed that the reaction occurred between the type-specific "M" substance and type-specific antibody, but more recent observations have indicated that this is not the case.

The nature of this antigen (hereafter called the "x" antigen) has been extensively studied in this laboratory. The work is not complete but certain essential details may be summarized. A full report will be presented elsewhere.

"x" antigen is regularly present in acid extracts of matt strains of Group A streptococcal cells of all types that have been examined. It is well preserved after removal of the group carbohydrate "c" by alcohol precipitation. The purified antigens prepared from strains of five types induced precipitation regularly with human sera collected during convalescence from infection with several types.

"x" antigen could not be detected if the extract were diluted 1:50 although "M" substance formed excellent precipitates with specific animal sera at dilutions of 1:1000. Various dilutions of the extracts were made between 1:50 and 1:500 and used in tests with sera obtained from patients convalescent from infection by streptococci of the homologous type. The presence of type-specific antibody was never demonstrated. These observations show that the reaction is not related to the M-anti-M antibody system.

Fractional alcohol precipitation was undertaken at various temperatures for the purpose of separating the type and group specific antigens present in the purified acid extract. This was never accomplished. All fractions in which an increased concentration of "M" substance was detected also contained a comparably increased amount of "x" antigen.

The anti-x antibody could be readily removed by adsorption to heat killed matt (M rich) and trypsin treated (M free) Group A hemolytic streptococcus cells but not to cells of *E. coli* or *Staph. aureus*. More detailed studies of this type are in progress.

The antigen used in the tests described in this paper was prepared as follows:

(1) Matt type 17 hemolytic streptococci, derived from 100 liters of veal infusion neopeptone broth, were extracted and purified by the method of Lancefield;<sup>39</sup> (2) the resulting material was precipitated in the presence of 3 volumes of 95 per cent ethyl alcohol and the precipitate recovered in 40 ml. of normal salt solution; (3) one volume of 95 per cent ethyl alcohol was added to the material, the precipitate removed in the centrifuge and discarded; (4) two additional volumes of alcohol were added to the supernatant obtained during step three. The resulting precipitate was recovered in 40 ml. of normal saline, preserved with merthiolate in a concentration of 1:10,000 and used for the tests.

Steps three and four were carried out throughout at the temperature of melting ice.

Precipitation did not occur when this material was tested in various dilutions against an animal serum containing large amounts of anti-c antibody. At a dilution of 1:1,000 it formed large amounts of precipitate with a type-specific anti-M serum prepared against a strain of type 17. At a dilution of 1:16, it reacted strongly with

the non-type-specific anti-x antibody present in the sera of human beings convalescent from infection by Group A hemolytic streptococci.

*The "C" Antigen.* The group specific "c" carbohydrate used for the tests to be described was obtained from Group A hemolytic streptococcal cells in a purified form by the method of Fuller.<sup>40</sup> The resulting fine, white powder was dissolved in normal salt solution of a concentration of .025 mg. per ml. for use in the tests.

#### SUMMARY

A substance is present in "M"-rich acid extracts of Group A hemolytic streptococcus cells which is not type-specific and is not the group specific "c" carbohydrate. This material forms precipitates with an antibody present in the serum of patients convalescent from infection by Group A streptococci. An extract containing this substance was prepared and used in association with a solution of purified "c" carbohydrate in a microprecipitin technic for the detection of antibodies in human sera.

#### ANTIBODY PHENOMENA

*Presence of Antibody at Onset of Infection.* Antibodies reacting with the "x" and "c" antigens were present in the sera from certain cases at the onset of the acute streptococcal illness. The former were detected in forty-five or 13.8 per cent, and the latter in forty-two, or 12.8 per cent, of 327 acute phase sera that were studied. These antibodies were present simultaneously in twenty-one cases. The antistreptolysin\* titers<sup>38</sup> of these sera were correlated with the presence or absence of the precipitating antibody. The derived data are summarized in Table 1.

The antistreptolysin titer was 100 units per ml. or less, in 61.7 per cent of those

\* The antibody studied was antistreptolysin "O".

TABLE I

CORRELATION OF ANTISTREPTOLYSIN TITERS AND PRECIPITIN TITERS OF ACUTE PHASE SERA

Precipitin Reaction	No.	Antistreptolysin titer in units per cc.											Titer 100 units or less		Titer 125 to 250 units		Titer 333 units or more	
		12	50	100	125	166	250	333	500	625	833	1,250	No.	%	No.	%	No.	%
X and C positive.....	21	0	1	3	6	6	2	0	1	1	0	1	4	19.0	14	66.6	3	14.3
X only positive.....	24	2	6	8	1	3	3	1	0	0	0	0	16	66.6	7	29.2	1	4.2
C only positive.....	21	3	5	3	8	2	0	0	0	0	0	0	11	52.4	10	47.6	0	0.0
X and C negative.....	256	52	65	41	43	37	12	2	2	2	0	1	158	61.7	92	35.7	6	2.3

sera in which no precipitating antibody was detected. In only 2.3 per cent was the antibody level greater than 250 units per ml. Comparable values were obtained when sera containing either x or c precipitin were studied. If both x and c precipitins were present, the results were different in that the antistreptolysin titer was 100 units per ml. or less, in 19.0 per cent and was greater than 250 units per ml. in 14.3 per cent. These are statistically significant variations.

A significant antistreptolysin response occurred in 54.5 per cent of those patients in which anti-x antibody was present and in 53.6 per cent of those in which anti-c antibody were present in the initial serum. (Table v.) This is a lower frequency of response than was observed among the group in which these antibodies were absent.

There was no relationship between the presence of either precipitin at the onset of acute streptococcal infection and the presence or absence of a positive Dick skin test.

Data presented in Tables II and IV demonstrate that, if either antibody was present in the initial sera, it was also present in sera obtained during the fourth week of the disease or later in nearly every case. By this time c antibody had disappeared in one and x antibody in five individuals.

One hundred forty-six acute phase sera

were obtained from patients suffering from non-streptococcal respiratory infections. Anti-x antibody was demonstrable in twenty-nine, or 19.8 per cent, of these, and anti-c antibody in thirty, or 20.0 per cent. The two antibodies occurred simultaneously in sixteen patients. These values are all slightly higher than those derived from the study of the streptococcal disease just described but the differences are not statistically significant.

*Antibody Response.* Serial determinations of the anti-x and anti-c antibodies were made in 278 cases of hemolytic streptococcus sore throat at intervals which permitted a comparative description of antibody response in these cases. Sera were collected on the second or third days of the acute illness, again between the eighth and tenth days and during the fourth week (twenty-one to thirty days). A smaller group was studied for a longer period. The essential data are summarized in Table II. There were, in addition, a number of patients in which the follow-up examination was not obtained until after the thirtieth day. These will be considered separately.

Neither antibody was initially present in 214 patients. When these men were re-examined during the fourth week, anti-x antibody had appeared in forty; anti-c in thirteen and both antibodies in fourteen. Anti-x, but not anti-c, antibody was



detected on the first examination in the sera of nineteen patients, in five of whom an anti-c response had occurred by the fourth week. Anti-x antibody disappeared in two cases. An anti-x antibody response was observed in six of seventeen cases in which anti-c antibody had been initially present.

situation prevailed in regard to the anti-c antibody in two cases. In both, antibody was still present during the sixth week.

The follow-up serum was obtained after the thirtieth day in certain patients. The data derived from a study of these patients are presented in Table III. Anti-x antibody

TABLE II  
ANTI-X AND ANTI-C ANTIBODY RESPONSE IN 278 PERSONS INFECTED BY HEMOLYTIC STREPTOCOCCI

Total Cases	Initial Serum																Initial Serum															
	Anti-X and anti-C antibody absent,				Anti-X antibody present. Anti-C antibody absent,				Anti-C antibody present. Anti-X antibody absent,				Anti-X and anti-C antibodies, present,				Anti-X antibody absent; all cases								Anti-C antibody absent; all cases							
	4th week serum				4th week serum				4th week serum				4th week serum																			
	Total cases				Total cases				Total cases				Total cases				Total cases								Total cases							
	X and C antibody absent	X antibody present	C antibody present	X and C antibody present	X antibody absent	X antibody present	C antibody absent	X and C antibody present	C antibody absent	C antibody present	X antibody absent	C and X antibody present	X antibody absent	X and C antibody present	X antibody present on day 8 to 10	X antibody present on day 21 to 30	X antibody response absent	C antibody present on day 8 to 10	C antibody present on day 21 to 30	C antibody response absent												
278	214	147	40	13	14	19	2	12	5	17	1	10	6	18	3	15	231	10	4.3	60	26.0	171	74.0	233	6	2.6	18	7.7	215	92.3		

There was a total of 231 patients in whom anti-x antibody was not discovered early in the disease. This antibody had appeared by the tenth day in ten, or 4.3 per cent, and by the fourth week in sixty, or 26.0 per cent. Anti-c antibody was not present in the initial serum from 233 patients. It had developed by the tenth day in six, or 2.6 per cent, and by the fourth week in eighteen, or 7.7 per cent.

Anti-x antibody was absent in the initial serum but present by the tenth day in six additional patients in whom the follow-up study was not done until the fifth to seventh weeks. At that time, four were still positive and two had become negative. A similar

developed in seven, or 20.0 per cent of thirty-four patients in this group in whom it was initially absent. The results of the study of anti-c antibody were similar except that an immune response occurred in five, or 12.8 per cent of thirty-nine patients.

Serial studies were available after the fourth week in twenty-seven patients in whom the anti-x, and in thirty-nine patients in whom the anti-c substances had not appeared within the first thirty days after the onset of the acute streptococcal disease. The data are presented in Table IV. Antibodies developed in four of each group although the studies were continued in several cases for more than fifty days.

Persistence of these antibodies was also studied in certain patients in whom these substances were initially present or developed during the first four weeks (Table iv). Anti-x antibody disappeared from the serum of two of a group of twenty-six patients, thirteen of whom were followed for more than forty-five days and nine for more than seventy days. Anti-c antibody persisted in all of fourteen cases in whom observations were available after the fourth week.

The presence of these antibodies clearly does not confer resistance against infection by Group A hemolytic streptococci, since they were initially demonstrable, either separately or together, in many men in whom an antistreptolysin response occurred, indicating that definite tissue invasion by these organisms had taken place. The frequency of antistreptolysin response was less in the men in whom these antibacterial antibodies were present at the onset of the acute illness, suggesting that a certain

TABLE III

ANTI-X AND ANTI-C ANTIBODY RESPONSE IN PATIENTS WITH LATE FOLLOW-UP ONLY

Initial Serum	Total Cases	Day of follow-up examination													
		31-35		36-40		41-45		46-50		51-60		61-70		71 and over	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-
X antibody absent.....	34	3	16	2	2	1	3	1	2	..	3	..	..	..	1
C antibody absent.....	39	3	19	1	5	..	3	1	4	..	3	..	..	..	

The development of precipitins has been compared with the frequency of significant antistreptolysin response. The data are presented in Table v. An increase in the latter antibody occurred in a comparable number of cases whether anti-x or anti-c precipitins did, or did not, appear during convalescence.

## COMMENT

As a result of the studies just described, it is possible to state that antibacterial antibodies, reacting with the "x" antigen and the "c" carbohydrate, were present in the sera of many men of military age at the onset of hemolytic streptococcal infection. These were not the non-specific precipitins of the type described by Tillet and Francis,<sup>41</sup> since they persisted into convalescence in nearly every instance in which observations were available at an appropriate time.

number of these cases were not actually instances of streptococcal respiratory disease. If this interpretation is correct, the hemolytic streptococci isolated from the throat and the antibodies discovered in the serum were the late results of a previous streptococcal infection.

Anti-x precipitins developed in approximately one-quarter, and anti-c precipitins in about 8 per cent of the members of this group of men infected by Group A hemolytic streptococci in whom these antibodies were not present at the onset of the illness. An antibody response had occurred in a few cases by the tenth day and was maximal by the end of the fourth week.

A small group of patients in whom precipitins had not appeared by the fourth week were followed for a longer period. The detection of only a few additional responses was accomplished by this procedure.

TABLE IV  
LATE DEVELOPMENT OR PERSISTENCE OF ANTIBACTERIAL ANTIBODIES IN PATIENTS WITH PROLONGED FOLLOWUP STUDY  
(Each patient recorded only once)

Initial Serum	Fourth Week Serum	Day of Followup Examination *													
		31-35		36-40		41-45		46-50		51-60		61-70		71 and over	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-
Anti-x Antibody															
Anti-X antibody absent	Anti-X antibody absent*	2	8	1	4	1	3	..	2	..	4	..	..	..	2
Anti-X antibody absent	Anti-X antibody present†	3	..	3	1	3	1	1	..	..	1	..	..	3	
Anti-X antibody present	Anti-X antibody present†	1	..	..	..	1	..	1	..	..	..	1	..	6	
Anti-c Antibody															
Anti-C antibody absent	Anti-C antibody absent*	1	10	..	6	1	3	..	3	1	4	1	2	..	7
Anti-C antibody absent	Anti-C antibody present†	2	..	2	..	3	..	..	..	..	..	..	..	4	
Anti-C antibody present	Anti-C antibody present†	1	..	1	..	..	..	..	..	..	..	..	..	1	

\* Last negative or earliest positive test recorded.  
† Last positive or earliest negative test recorded.

Actual infection by hemolytic streptococci occurred in the men in whom no precipitins developed, since the frequency of significant antistreptolysin response in this group was similar to that observed in those cases in which either anti-x or c antibody developed.

The duration of the follow-up study was insufficient to determine the total length of time that anti-x and anti-c antibodies might persist in the serum when initially present or after their appearance as the result of infection. These antibodies disappeared in only two of a small group of patients who were studied from forty-five to seventy days after the acute illness.

RELATIONSHIP OF ANTIBODY PHENOMENA TO NATURE OF DISEASE

The relationship of the initial presence or the later development of the anti-x and

anti-c antibodies to the nature and course of hemolytic streptococcus sore throat has been evaluated and the results presented below.

*Acute Illness.* The maximum recorded temperature, duration of fever, total leukocyte count, initial and follow-up (fourth week) and erythrocyte sedimentation rates (Westergren) were compared with the presence or absence of anti-x or anti-c precipitins at the onset of the disease. Information was available in 335 cases of Group A streptococcal respiratory disease. This analysis failed to reveal a correlation in any category of clinical or laboratory signs between the presence or absence of these antibodies and the nature or course of the acute suppurative phase of the illness. The data on which this statement is based have not been presented in this paper.

TABLE V

COMPARISON OF THE FREQUENCY OF SIGNIFICANT ANTISTREPTOLYSIN RESPONSE WITH THE PRESENCE OR DEVELOPMENT OF ANTI-X OR ANTI-C PRECIPITINS

Initial Serum	Followup Serum	Number of Cases	Significant Antistreptolysin Response	
			Number	Per Cent
X antibody absent	X antibody absent	172	136	79.1
X antibody absent	X antibody present	75	62	82.7
X antibody present	X antibody present	44	24	54.5
C antibody absent	C antibody absent	237	191	80.6
C antibody absent	C antibody present	40	31	77.5
C antibody present	C antibody present	41	22	53.6

Cases in which anti-x and anti-c antibody developed during convalescence were also studied to determine whether the appearance of these antibodies was related to the severity of the acute disease as measured by the clinical and laboratory information just described. No correlation in any category was discovered between antibody response and the nature of the initial illness.

*Suppurative Complications.* Twenty-nine of the cases in whom suitable serial precipitin determinations were available had suffered from a definite suppurative complication of hemolytic streptococcal sore throat.<sup>35</sup> The initial disability in these patients was prolonged and accentuated as a result of otitis media, peritonsillar abscess or sinusitis. In spite of this fact, examination of Table vi reveals that anti-x and anti-c antibodies were present at the onset of the disease or developed during convalescence with the same frequency among these cases as in the group as a whole.

*Non-suppurative Complications.* A considerable number of hemolytic streptococcal

TABLE VI

RELATIONSHIP OF SUPPURATIVE COMPLICATIONS TO PRESENCE OR DEVELOPMENT OF ANTI-X OR ANTI-C ANTIBODIES

	Suppurative Complications		All Cases	
	No.	Per Cent	No.	Per Cent
X Antibody				
Total . . . . .	29	100.0	298	100.0
Always absent . . . . .	21	72.4	196	65.7
Present initially . . . . .	3	10.3	37	12.4
Developed during convalescence . . . . .	5	17.2	65	21.8
C Antibody				
Total . . . . .	29	100.0	298	100.0
Always absent . . . . .	24	82.8	244	81.9
Present initially . . . . .	2	8.3	35	11.7
Developed during convalescence . . . . .	3	10.3	19	6.4

respiratory infections in this study group initiated pathological processes, apparently of a non-suppurative nature. Clinical manifestations of these disorders were arthritis with or without fever, or carditis (rheumatic fever), late fever with or without carditis, carditis without fever or arthritis and pneumonitis with or without carditis.<sup>36</sup> All of these syndromes may well have a common pathogenesis.<sup>1</sup> The data derived from a study of these cases have been analyzed in relation to the presence or development of precipitating antibodies to determine whether the presence or absence of these substances might be related to the appearance of these complications. Other post-streptococcal phenomena, perhaps less clearly allied to these disorders, such as late adenitis, have been omitted.

The essential data are presented in Table vii. The total number of cases is larger than that described in Table ii since patients were included for the purpose of this analysis in whom the first follow-up observation was not made until after the fourth week. (Table iii.)

TABLE VII  
RELATIONSHIP BETWEEN THE INITIAL PRESENCE OR LATER DEVELOPMENT OF ANTI-X AND ANTI-C ANTI-BODIES AND THE FREQUENCY OF OCCURRENCE OF NONSUPPORTIVE POSTSTREPTOCOCCAL COMPLICATIONS

	Complications			Antibody Status						Antibody Status					
				X Antibody Never Present			X Antibody Present Initially			X Antibody Developed during Convalescence			G Antibody Never Present		
	No. of Cases	Per Cent of All Cases		No. of Cases	Per Cent Total in This Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Category	Per Cent of Complication
Arthritis.....	18	6.0		3	1.5	16.7	7	18.9	38.9	8	12.3	44.4	10	4.1	55.6
Late fever.....	13	4.4		11	5.6	84.5	0	0.0	0.0	2	3.1	15.5	13	5.3	100.0
Carditis, all cases.....	16	5.4		9	4.6	56.2	1	2.7	6.2	6	9.2	37.5	11	4.5	68.7
Carditis with late fever.....	6	2.0		5	2.6	83.4	0	0.0	0.0	1	1.5	16.6	6	2.5	100.0
Carditis without late fever.....	10	3.4		4	2.0	40.0	1	2.7	10.0	5	7.7	50.0	5	2.0	50.0
Pneumonitis.....	3	1.0		0	0.0	0.0	0	0.0	0.0	3	4.6	100.0	2	0.8	66.3
All complications.....	44	14.8		18	9.1	40.9	8	21.6	18.2	18	27.7	40.9	30	12.3	63.4
Total uncomplicated.....	254	85.2		178	90.9	70.0	29	78.4	11.4	47	72.3	18.6	214	87.7	84.3
Total cases.....	298	100.0		196		65.7*	37		12.4*	65		21.8*	244		81.9*

\* Per cent of total cases.  
(Read columns headed “% total in this antibody category” vertically.)  
(Read columns headed “Per cent of complication” horizontally.)

*Arthritis.* Arthritis of varying degrees of severity followed the initial hemolytic streptococcus sore throat in eighteen, or 6.0 per cent of all cases. x antibody was never demonstrated in the sera of three (Cases 3, 4, and 11<sup>36</sup>); it was present at the onset of the acute sore throat in seven (Cases 2, 7, 8, 12, 13, 16, and 17<sup>36</sup>) and it appeared during convalescence from the initiating streptococcal infection in eight (Cases 5, 6, 9, 10, 14, 15, 18, 19<sup>36</sup>). This antibody was either initially present or developed later in 83.3 per cent of the patients with an involvement of the joints. Anti-x precipitin was discovered early or during convalescence in only 30.0 per cent of the uncomplicated and in 34.2 per cent of all the patients.

If each antibody category is considered, 1.5 per cent of those in whom anti-x antibody was never present, 18.9 per cent of those in whom it was detected in the initial serum and 12.3 per cent of those in whom it appeared later developed arthritis. This complication occurred ten times as frequently when anti-x antibody was present early or appeared later. The differences just described are statistically significant. It was previously noted that an antistreptolysin response occurred less frequently in those patients in whom the x antibody was initially present. Thirty-five per cent of this group in whom infection by streptococci could be established by the appearance of increased amounts of antistreptolysin developed arthritis.

If the anti-x precipitin appeared during convalescence from the acute respiratory illness, it was invariably demonstrable at the end of the third, or early in the fourth week and was always present at the time when arthritis became manifest. The three patients in whom this precipitin was never discovered were followed for fifty-seven, seventy-four and 132 days until recovery from the arthritic process which was severe

or moderately severe in all. The possibility of a late antibody response in these patients has been excluded.

When the anti-x antibody had appeared in these arthritic patients it persisted in fourteen of fifteen patients throughout the period of observation which varied from thirty-nine to 160 days, with a mean of eighty-five days, after the onset of the initiating streptococcal disease. Disappearance of the antibody was noted in one case between the forty-ninth and fifty-seventh days.

Table vii also demonstrates the frequent occurrence of anti-c precipitins either initially or during convalescence in post-streptococcal arthritis. It will be noted that there were ten cases in which this antibody was always absent. x antibody was demonstrated in seven of the remaining eight. This is a more frequent simultaneous occurrence of the two antibodies than for the whole group (65 per cent of all cases in which anti-c antibody was demonstrated) but the difference may be the result of the statistical errors of small groups.

*Late Fever.* A febrile illness which followed hemolytic streptococcus sore throat after a latent or quiescent period of five to nineteen days in length and often associated with electrocardiographic evidence of carditis was frequently observed during this study.<sup>36</sup> It has been regarded as a disorder similar in pathogenesis to the arthritic disease just discussed.

The data in Table vii reveal that, from an immunological standpoint, the two disorders are very different. Anti-x precipitins were rarely (15.5 per cent) and anti-c precipitins at no time demonstrated in the sera of patients in whom late fever supervened. Electrocardiographic evidence of carditis was detected in six of these patients, in one of which anti-x precipitin was present at the onset of the acute streptococcal disease.

*Carditis.* Carditis with late fever has just been described. In addition, abnormal electrocardiograms were discovered in ten cases during convalescence from the initial streptococcal infection in the absence of arthritis or late fever. Anti-x antibody was detected in the serum obtained at the onset of the acute respiratory infection in one and appeared during convalescence in five other cases. The frequency of occurrence of this precipitin in these individuals is greater than that for the whole group but the differences are not statistically significant and are not comparable with those observed when arthritis was present. It may be worth while to note that electrocardiographic evidences of carditis were not marked and the duration of carditis was short in three (Cases 3, 15 and 20<sup>33</sup>) of the four cases in which x-antibodies were never detected. Anti-c antibodies were demonstrable in the initial serum of four and developed during convalescence in one of these examples of poststreptococcal carditis. There was an associated occurrence of anti-x antibody in four of these cases. This situation, therefore, closely parallels that observed in the arthritic group.

*Pneumonitis.* A pneumonitis believed to have been non-suppurative complicated the course of three cases of streptococcal sore throat.<sup>36</sup> Anti-x antibody developed during convalescence from the initial illness in all of these individuals.

#### COMMENT

The observations just described have demonstrated that there was no correlation between the nature or severity of the acute suppurative phase of hemolytic streptococcus sore throat and the presence of antibacterial precipitating antibodies at the onset of the disease or their appearance during convalescence.

A striking relationship was discovered between the occurrence of these antibodies

and the development of the late non-suppurative complications of the post-streptococcal state. The anti-x precipitin was demonstrable in the sera obtained at the onset of the streptococcal respiratory disease or in those obtained during convalescence from it in fifteen, or 83.3 per cent of eighteen cases of poststreptococcal arthritis. A similar correlation was observed between the presence of this antibody and of poststreptococcal non-suppurative pneumonitis. An analogous but less definite relationship was observed with regard to non-febrile poststreptococcal carditis. Anti-x antibody was rarely demonstrated at any time during the course of hemolytic streptococcus sore throat complicated by a late, presumably non-suppurative, febrile illness with or without carditis.

Previous investigators<sup>14,18</sup> believed that a precipitin, apparently the same as that described as the x antigen in this paper, was delayed in its development if arthritis supervened following hemolytic streptococcal respiratory disease. This was not the case in this group.

#### GENERAL DISCUSSION

The results of many investigations<sup>1</sup> have established the fact that there is an intimate relationship between Group A hemolytic streptococcal disease, particularly of the upper respiratory tract, and the rheumatic state. It was demonstrated in a recent critical study<sup>1</sup> that arthritis was a sequel to respiratory infection only when the etiological agent of the initiating disorder was the hemolytic streptococcus and that a non-arthritic, continuing pathological process with or without carditis often followed diseases caused by these organisms.

Considerable indirect evidence indicates that these serious late non-suppurative complications of hemolytic streptococcal infection are the result of an immunological process, probably analogous to serum sick-

ness. The suggestion has been made that sensitization of human beings occurs as the result of exposure to some fraction or product of hemolytic streptococci and that this substance must be common to all or, at least, to many different types or strains of Group A hemolytic streptococci because complications follow infection or reinfection by different strains or types of these organisms.<sup>1</sup>

Among the known possible sensitizing proteins elaborated by Group A streptococci are the erythrogenic toxin, the serum protease activating substance usually called fibrinolysin, streptolysins "o" and "s," the "x" substance described in this paper, the "c" carbohydrate as it occurs in antigenic combination with protein in the bacterial cell and the various nucleoproteins of Heidelberger.<sup>10</sup> The "m" and "r" substances would not seem suitable since they are type specific and dissimilar in different strains. For reasons to be detailed elsewhere, it is probable that the four "exotoxins" just listed are not involved in the pathogenesis of the poststreptococcal state.

This paper describes a study of two substances extracted from the streptococcal cell, both of which are group rather than type specific, and which might therefore be sensitizing agents capable of inciting the phenomena of the poststreptococcal state. One was the well known "c" carbohydrate; the other, the "x" substance is present in acid extracts of Group A streptococcal cells and forms non-type-specific precipitates with sera obtained from certain normal human beings and from others convalescent from hemolytic streptococcal infection. The nature of this antigen is, as yet, undefined. It is closely associated with the type specific "m" substance from which it has not been possible to separate it by chemical methods, and may well be the "nucleoprotein" which has been described by Zittle in "m" extracts.<sup>42</sup>

If the pathogenesis of these disorders is the result of an immunological reaction of the anaphylactic type, it is reasonable to suppose that a circulating antibody might be present in serum obtained from affected persons which would be capable of reacting with the sensitizing antigen, as is the case in serum sickness.<sup>43</sup> The present investigation is the result of a search for such an immune substance.

Antibodies reacting with the "c" carbohydrate or "x" protein were present in approximately 15 per cent of cases of acute streptococcal respiratory disease at the onset of the illness and cannot be regarded as conferring protection against tissue invasion by these organisms. Anti-x precipitin appeared during convalescence in the sera of approximately 22 per cent, and anti-c precipitin in approximately 6 per cent of the remaining patients. Antibody response was nearly maximal by the end of the fourth week.

The nature and severity of the acute suppurative phase of hemolytic streptococcal sore throat was not altered by the initial presence or later development of either of these antibodies. A different situation prevailed in regard to non-suppurative complications. Anti-x antibody was present at the onset of the sore throat or later in fifteen of eighteen individuals in whom arthritis was a sequel to hemolytic streptococcal respiratory disease; 14.7 per cent of cases in whom this precipitin was at some time demonstrated developed involvement of the joints; only 1.5 per cent of those in whom it was not demonstrated did so. These differences are of statistical significance and there can be no doubt that the presence of this antibody is, in some way, related to the rheumatic state. Additional studies not reported here of sera obtained from other cases of rheumatic fever in military personnel, in whom the initiating streptococcal infection had not been ob-



served, confirm this fact.<sup>44</sup> An anti-x antibody response also occurred in all of three cases of non-suppurative poststreptococcal pneumonitis.

A similar but less striking correlation was discovered between the presence of x antibody and afebrile poststreptococcal carditis. The precipitin was rarely demonstrated in sera from patients in whom poststreptococcal fever occurred. The arthritic and non-arthritic poststreptococcal disorders have been previously regarded as of a similar pathogenesis although clinical study showed that involvement of the joints was associated with a more severe process. Definite evidence is presented here which establishes an immunological difference between the two syndromes.

Anti-c antibody was not discovered more frequently in complicated than in uncomplicated streptococcal disease except in a few arthritic cases in which it occurred in association with the x antibody. It is not believed to be related to poststreptococcal non-suppurative disease.

Discussion of the manner in which the x antigen may be involved in the pathogenesis of poststreptococcal arthritis must be speculative. It is possible that this substance is the sensitizing antigen and that its antibody is responsible for the development of the rheumatic state.

If the x substance is not the sensitizing agent, the presence of its antibody in these cases may merely mirror a general increase of immunological response on the part of these human beings to streptococcal products which places them in a group in which arthritis caused by hypersensitivity phenomena is more likely to appear following streptococcal infection. This hypothesis becomes less tenable when it is known that these same individuals did not produce antistreptolysin or antifibrinolysin in unusually large amounts<sup>45,46</sup> as the result

of the initiating hemolytic streptococcus infection.

It is also possible that the development of anti-x antibody is related in some non-specific way to disease of the joints since it, or a closely related precipitin, is often demonstrable in the serum of patients suffering from rheumatoid arthritis, a disease whose pathogenesis may be different from that operative in poststreptococcal arthritis.

The validity of any of these hypotheses cannot be determined at the present time. The first is most attractive and opens more promising avenues for future investigation.

The absence of the anti-x antibody from the sera of patients suffering from poststreptococcal fever is disturbing, since this syndrome was believed<sup>1</sup> to be the result of a pathological and immunological process similar to that causing the arthritic disease. This point of view may not be correct, but it is also possible that differences noted are quantitative rather than qualitative. The suggestion has already been made on the basis of bacteriological and clinical information<sup>1,36</sup> that arthritic poststreptococcal disease was associated with a greater degree of hypersensitivity requiring repeated infection by hemolytic streptococci in certain patients. The absence of anti-x antibody in many poststreptococcal fevers may indicate that the reaction in these individuals was insufficiently violent to produce a measurable excess of antibody in the circulating blood. This would be in approximate accord with observations in horse serum sickness<sup>43</sup> in which large amounts of anti-horse serum precipitin appeared when the disease was severe and small amounts or none when it was mild.

An important difference exists between the phenomena described here and those previously reported in serum sickness.<sup>43</sup> Anti-horse serum precipitins were not demonstrable until the clinical manifesta-

tions of the immunological disorder had abated although the sensitizing antibody must have been present for a much longer time. Precipitin was not measurable in the circulating blood until the huge quantity of antigen (horse serum) had been either immunologically neutralized, metabolized or excreted. Excess sensitizing antibody might be expected to appear earlier in the serum of human beings infected with hemolytic streptococci since the amount of antigen capable of neutralizing antibody *in vivo* is much smaller than in serum disease.

Earlier investigators have stated that the production of anti-x antibody or a closely related substance was delayed following hemolytic streptococcus sore throat if rheumatic fever was a complication.<sup>14,18</sup> This observation has not been confirmed by the present study. The reason for this discrepancy is not apparent but it is possible that the method was capable of detecting antibody in smaller amounts than the technic used by other workers.

Another detailed investigation<sup>5</sup> of precipitating antistreptococcal antibodies failed to reveal any significant differences between the occurrence of these substances in streptococcal respiratory disease with or without complicating rheumatic fever. The tests were made with extracts of streptococcal cells containing "c" carbohydrate and nucleoprotein but not those known to contain the "x" antigen. These observations confirm the results of the present work in regard to the "c" carbohydrate and suggest that the nucleoproteins soluble at neutrality or in alkali also are not involved in the causation of streptococcal hypersensitivity.

The information obtained during this investigation does not justify further conjecture in regard to the pathogenesis of the non-suppurative complications of the post-streptococcal state. It is quite possible that the "x" substance described here is the

substance responsible for the stimulation of Group A streptococcal hypersensitivity in human beings. Theoretical and experimental considerations permit the tentative exclusion of several streptococcal products from a rôle in these hypersensitivity reactions.

Many protein and at least one carbohydrate (hyaluronic acid) fractions of the streptococcal cell, in addition to the two described in this paper, have not been fully evaluated in relationship to their rôle in the causation of hypersensitivity in man.\* The use of all the substances in chemically purified form as materials for injection into human beings and in immunological investigations of the type described in this paper might conclusively indict the "x" or another substance as the sensitizing antigen responsible for the incitement of post-streptococcal disease. Further progress toward the recognition, understanding and control of late non-suppurative complications of streptococcal infection awaits this event.

#### SUMMARY

1. Purified c carbohydrate and a non-type-specific "x" substance present in acid extracts of Group A hemolytic streptococcal cells have been used in precipitin tests with human sera.

2. Antibodies against one or the other or both of these antigens were demonstrable in the sera of certain cases of acute streptococcal sore throat at the onset of infection.

3. An anti-c antibody response occurred in 6 per cent of the patients, and an anti-x antibody response occurred in 22 per cent of the men infected by Group A hemolytic streptococci.

4. The presence or development of neither antibody could be correlated with any

\*The author believes that investigation of this problem in animals other than man and, possibly other anthropoids, will be disappointing because hypersensitivity states are strikingly different among various mammalian species.

aspect of the acute suppurative phase of the illness.

5. Poststreptococcal arthritis and pneumonitis occurred more frequently in infected men in whom anti-x antibody was demonstrable in the initial serum or during convalescence than in those in whom it was not present. A similar relationship was not discovered for anti-c precipitin.

6. Anti-x antibody was infrequently discovered during the course of streptococcal respiratory disease complicated by late fever.

7. It is suggested that the "x" substance may be the antigen responsible for serious streptococcal hypersensitivity.

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# Auricular Electrogram in Parasternal Leads\*

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THE clinical information which the electrocardiogram is able to furnish regarding the size and function of the auricles has been largely limited to studies of the standard limb leads. However, the composite picture of auricular activity as represented in these leads fails to yield the specific information which might be secured from direct leads. Leads from parasternal interspaces have been found of value in recording the variations in potential from the right auricle. Intrinsic deflections, characteristic of direct leads from the auricular surface, can be obtained from these semi-direct leads and satisfactorily correlated with clinical and roentgenological findings. Their interpretation is in accord with the experimental work of Sir Thomas Lewis and of Frank Wilson and his co-workers.

Special precordial leads have frequently been used to increase the amplitude of auricular waves in flutter, fibrillation and in tachycardias of indeterminate origin. Lewis<sup>14</sup> observed maximal oscillations when the electrode was placed over the right auricle in cases of fibrillation, and pointed out that enlargement of this chamber was a factor in obtaining augmented waves. Evans<sup>8</sup> and Szekely<sup>18</sup> failed to recognize any close relationship between the size of the auricular waves in fibrillation and the degree of right auricular enlargement. Drury and Iliescu,<sup>6</sup> using sternal and antero-posterior leads, found that coarse auricular deflections were obtained when the exploring electrode was placed to the right of the sternum. Lian and Pinchenzon<sup>16</sup> placed electrodes over the manubrium and paired

these with leads from the right fifth interspace. Similarly, Schoenewald<sup>17</sup> obtained clear, upright P waves in leads from the third right interspace to the right arm. Szekely,<sup>18</sup> following the suggestion of Faulkner<sup>9</sup> and Williams and Ellis,<sup>19</sup> was able to determine the origin of obscure tachycardias by leads from the third right interspace, paired alternately with the right arm and the left leg; Barker, Wilson, Johnston, and Wishart<sup>2</sup> took leads from the upper sternum to the ensiform to demonstrate certain types of auricular tachycardia.

We have recently reported two cases of tricuspid insufficiency<sup>7</sup> in which large, sharply diphasic auricular waves with intrinsic deflections were found in parasternal leads, using the left leg position for the indifferent electrode. Similar conspicuous diphasic P waves in leads from the right precordium have been described by Gertz<sup>10</sup> and by Burton and Mehlman.<sup>5</sup> In both instances, however, an extracardiac factor produced a displacement of the heart, bringing the right auricle in close juxtaposition to the anterior chest wall.

In the cases studied at Toledo Hospital there has been found a close relationship between the degree of right auricular enlargement and the size and character of the auricular complexes in parasternal leads. Not only does the size of these waves conform to clinical findings of hypertrophy and dilatation, but the variations in form yield information as to the location and extent of the anterior wall of the right auricle. A large number of observations have been made on normal hearts and on those show-

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ing demonstrable right auricular strain. The taking of three leads from each parasternal interspace, paired successively with the right arm, the left arm and the left leg, presents a sequence in which the lead paired with the right arm gives the strongest positive auricular deflection, and that connected with the left leg gives the strongest negative auricular deflection, while the lead paired with the left arm occupies an intermediate position. (Figs. 1, 2 and 3.) This sequence has also been recorded by Hecht<sup>11</sup> and is dependent upon the auricular potential of the extremity used for the indifferent electrode.

When the influence of the indifferent electrode is greatly reduced by the use of the central terminal, according to Wilson's method, the auricular wave in parasternal leads assumes a diphasic (+ -) pattern whenever the exploring electrode is directly over and in close proximity to the anterior wall of the right auricle. The relative value of the positive and negative elements is significant, and, since it represents the changes in potential from that part of the auricle directly beneath the electrode, the distance from the sinoauricular node determines the character of the wave. The greater the distance from the sinoauricular node to that portion of the auricle directly beneath the electrode, the greater is the duration of the pre-intrinsic component and the higher is the upward deflection of the diphasic wave. Conversely, the closer the exploring electrode is to the point of origin of the excitatory impulse, the shorter is the pre-intrinsic phase and the sooner will the abrupt fall of the intrinsic deflection occur. This conforms to the findings of Lewis<sup>15</sup> and Wilson and his co-workers<sup>20</sup> in leads taken directly from the wall of the right auricle and to the observations of W. Hurst Brown<sup>3,4</sup> in his study of the esophageal lead. Unipolar parasternal leads in Figures 3 and 4 yield these diphasic auricu-

lar waves with the characteristic intrinsic deflection and show the variations in size and form which occur with changes in the location of the exploring electrode.

For clinical purposes, insofar as the auricular complex is concerned, parasternal leads paired with the left arm may be used in place of the unipolar leads and yield similar records as is well illustrated in Figures 2 and 3. This is presumably due to the balanced potentials of the auricular deflections as registered in unipolar left arm leads. The same is true of the Wolferth leads so arranged that the exploring electrode is placed in the parasternal interspaces and the indifferent electrode posteriorly in the interscapular space. Wolferth parasternal leads are illustrated in Figure 5.

To illustrate the character of these semi-direct electrograms the following selected cases of right auricular strain are briefly presented, together with chest films and electrocardiograms. In all tracings the galvanometer was standardized at normal sensitivity (1 mv. = 1 cm.), and a chest electrode 2.5 cm. in diameter was used in taking the parasternal leads.

#### CASE REPORTS

CASE I. Bronchiectasis: T. L., a fifty-three-year-old white male, was admitted to Toledo Hospital in November, 1945. His chief complaint was a persistent cough of two years' duration with copious amounts of purulent sputum. He was known to have a moderate hypertension of long standing. There was no history of a coronary occlusion. Aside from a few musical rales there were no abnormal findings in the lungs, and the remainder of the physical examination was normal. The sputum contained numerous polymorphonuclear leukocytes, two per cent of which were eosinophiles. No acid-fast bacilli were discovered. The blood picture and urinalysis were within normal limits.

Films of the chest (Fig. 1) show moderate cardiac enlargement and emphysema of the

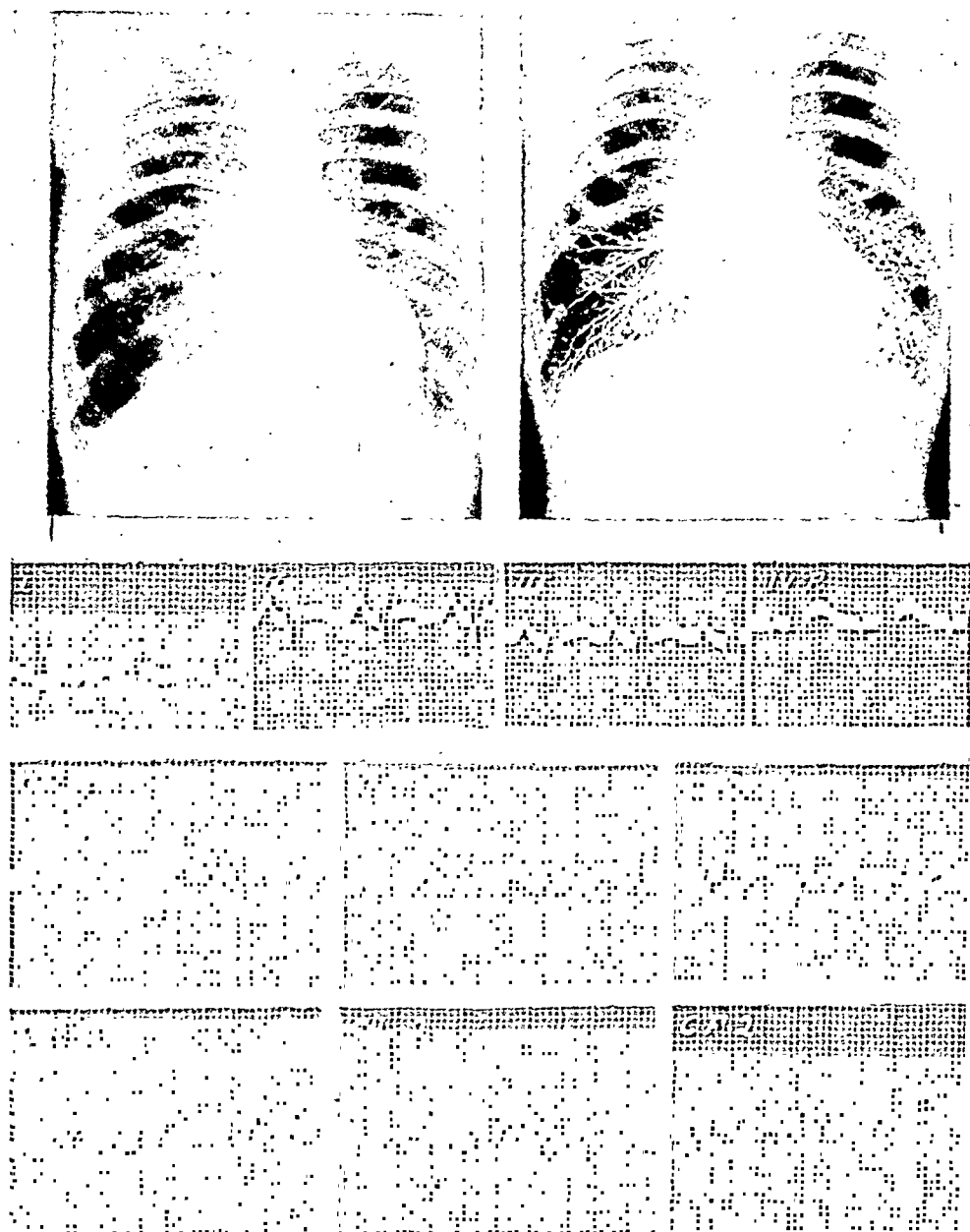


FIG. 1. Case I, chest film shows emphysema of the right base and left ventricular hypertrophy. Bronchogram shows bronchiectasis, mainly of the left lower lobe. Standard leads show large P waves in leads II and III and double R waves in II and IV-F. The negative effect of the left leg electrode and the positive effect of the right arm electrode on parasternal P waves is illustrated. Intrinsic auricular deflections occur in the fourth interspace to the left as well as to the right of the sternum.

right base. The increase in convexity of the left cardiac contour is evidence of left ventricular hypertrophy. A bronchogram shows sacular bronchiectasis chiefly of the lower left lobe.

The standard leads of the electrocardiogram are bizarre, and although the first lead is suggestive of an anterior infarction, the character of the QRS complex in the limb and precordial leads is evidence of an intraventricular

conduction defect of the left bundle branch type. Auricle hypertrophy of the cor pulmonale pattern<sup>13</sup> is indicated by broad, high P waves in leads II and III. The parasternal leads show the sequence previously described, the P waves being most positive in CR-1 and CR-2, most negative in CF-1 and CF-2 and approximately equiphase in CL-1 and CL-2. The finding of characteristic diphasic auricular waves in CL-1

and CL-2 with abrupt intrinsic deflections from both sides of the sternum indicates considerable enlargement of the right auricle and its proximity to the anterior chest wall beneath the fourth right and left interspaces.

CASE II. Pulmonary infarct: Dr. W. D., a dentist, 63 years of age, was admitted to Toledo Hospital in November, 1945. Until two months previously he had enjoyed excellent health. During the last two months he had become increasingly short of breath, and several days prior to admission he noted a productive cough with blood-tinged sputum and chest pains on deep breathing.

Physical examination showed a temperature of 101°F a pulse of 120, respirations 40 and a blood pressure of 150/105. Dullness and increased vocal fremitus were found in the right base posteriorly. Râles were present in both apices and scattered throughout the left side. The heart was moderately enlarged. There were no murmurs. The liver was palpable 2 cm. below the costal margin. There was no edema, and the examination was otherwise normal. The leukocyte count on admission was 12,000 with 86 per cent polymorphonuclears. There was no anemia. The urine contained a trace of albumin, and the blood nonprotein nitrogen was slightly elevated. Blood cultures were negative. There were a few gram-positive cocci in the sputum which were not pneumococci. The clinical diagnosis was pneumonia of the right lower lobe and cardiac hypertrophy with moderate decompensation.

The patient's course in the hospital was stormy. Although the pneumonic process cleared under penicillin therapy, his cough and dyspnea continued. He was digitalized with some improvement. Two episodes of intense pain were interpreted as splenic and pulmonary infarctions.

The chest film reproduced (Fig. 2) was taken after resolution of the pneumonia and the absorption of a small amount of pleural fluid seen in previous films. The heart shows enlargement in all diameters and extends some distance to the right of the sternum. The aortic shadow is broad and heavy. There is a single infarct in the right middle lobe. The chest is otherwise clear.

Electrocardiograms show left axis deviation in the standard leads, large P waves, prolonged auriculo-ventricular conduction time (0.22 sec.) and evidence of diffuse myocardial damage. Parasternal leads from the fourth interspace when connected with a left arm electrode and with a unipolar central terminal, show the characteristic diphasic wave with the sharp intrinsic deflection of a semidirect auricular electrogram. A smaller diphasic wave is seen in a lead from the left of the sternum. It is evident that the right auricle is in close apposition to the anterior chest wall at these points. This may have been the result of the stress placed on the right side of the heart by acute pulmonary disease, or it may have resulted from the general cardiac hypertrophy producing a forward displacement of an already enlarged auricle. Electrocardiograms including parasternal leads taken in June, 1946, six months after the records shown in Figure 2, show much smaller, less abrupt parasternal P waves and support the former interpretation.

CASE III. Rheumatic endocarditis: R. McK., seven years of age, was admitted to Toledo Hospital in January, 1946. Infancy and childhood had been normal until the age of four when he developed Sydenham's chorea, and a heart murmur was discovered. Upon recovery his tonsils and adenoids were removed. A second attack of chorea occurred at the age of six. He was kept in a convalescent home for twelve months and given prophylactic sulsonamide therapy. Two weeks prior to admission his nervous symptoms recurred for the third time. There had been no arthritic manifestations.

Examination revealed a mildly febrile white boy with a slight speech defect and occasional twitching of the shoulders, arms and hands. The throat was injected. The chest was normal. The pulse was regular but rapid. The heart was not appreciably enlarged. There was a blowing systolic murmur, grade 3, audible over the entire precordium, but loudest at the apex. A soft mid-diastolic murmur was present which was accentuated in the left lateral position. The clinical impression was recurrent Sydenham's chorea with rheumatic carditis and involvement of the mitral valve.

Chest films show a moderate cardiac enlarge-



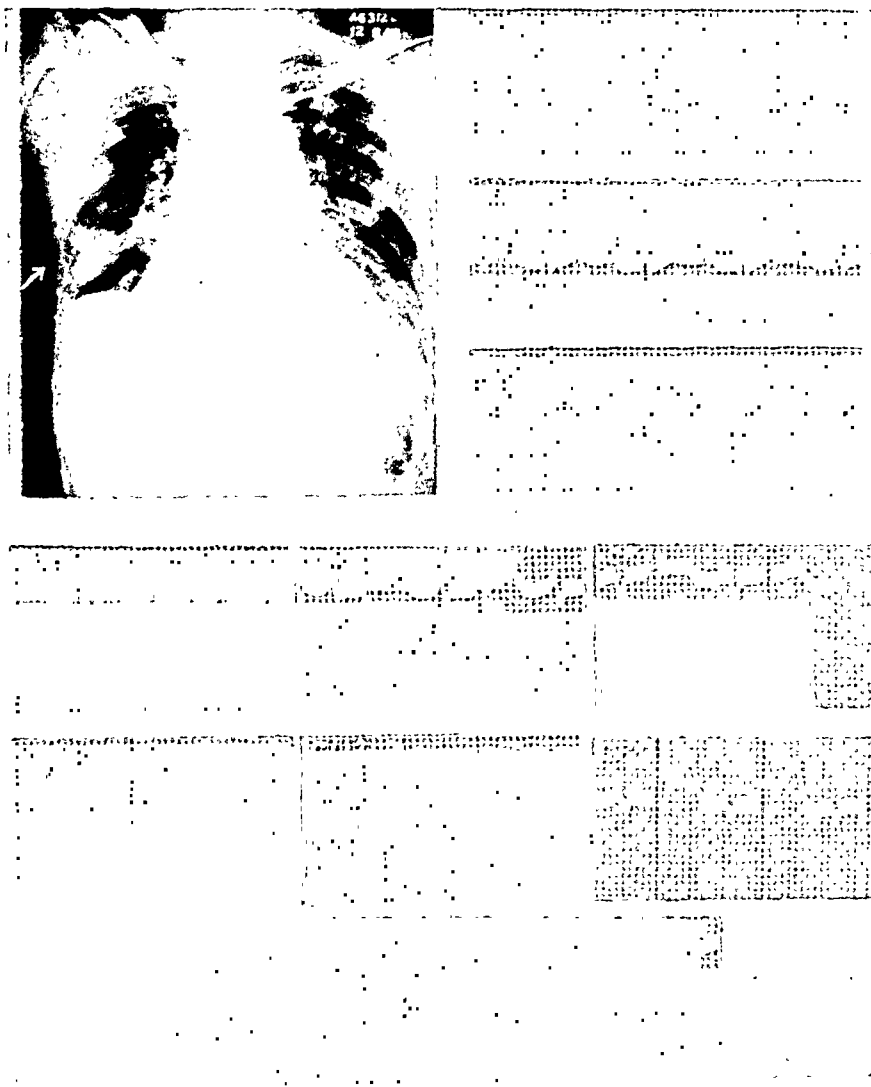


FIG. 2. Case II, chest film shows general cardiac hypertrophy with widening of the aortic shadow and the residual changes following a pulmonary infarct. Standard leads show left axis deviation, evidence of myocardial damage, prolonged P-R interval and large auricular waves in lead II. Intrinsic auricular deflections are conspicuous in CL-1 and unipolar lead V-1. A smaller diphasic P wave is present in CL-2.

ment with some fullness in the pulmonary conus but no other abnormality. The limb leads of the electrocardiogram show a right axis deviation and a prolonged auriculoventricular conduction time (0.24 sec.). There are large P waves in leads I and II which conform to the mitral pattern of auricular hypertrophy. Four leads were taken from each parasternal interspace by changing the site of the indifferent electrode and by using Wilson's central terminal. (Fig. 3.) The similarity between unipolar parasternal auricular complexes and those obtained by using the left arm as the site of the indifferent

electrode is illustrated. The pull toward positivity when the right arm is coupled with the parasternal leads, and the negative effect of the left leg electrode on the parasternal auricular deflection is also shown.

Diphasic waves from the right auricle with abrupt intrinsic deflections were obtained from the third and fourth interspaces, both to the right and to the left of the sternum. These are clearly seen in CL-4th R (CL-1), V-4th R (V-1), CF-4th L (CF-2), CL-3rd L, and V-3rd L. From the character of these auricular waves and the positions from which they were obtained,

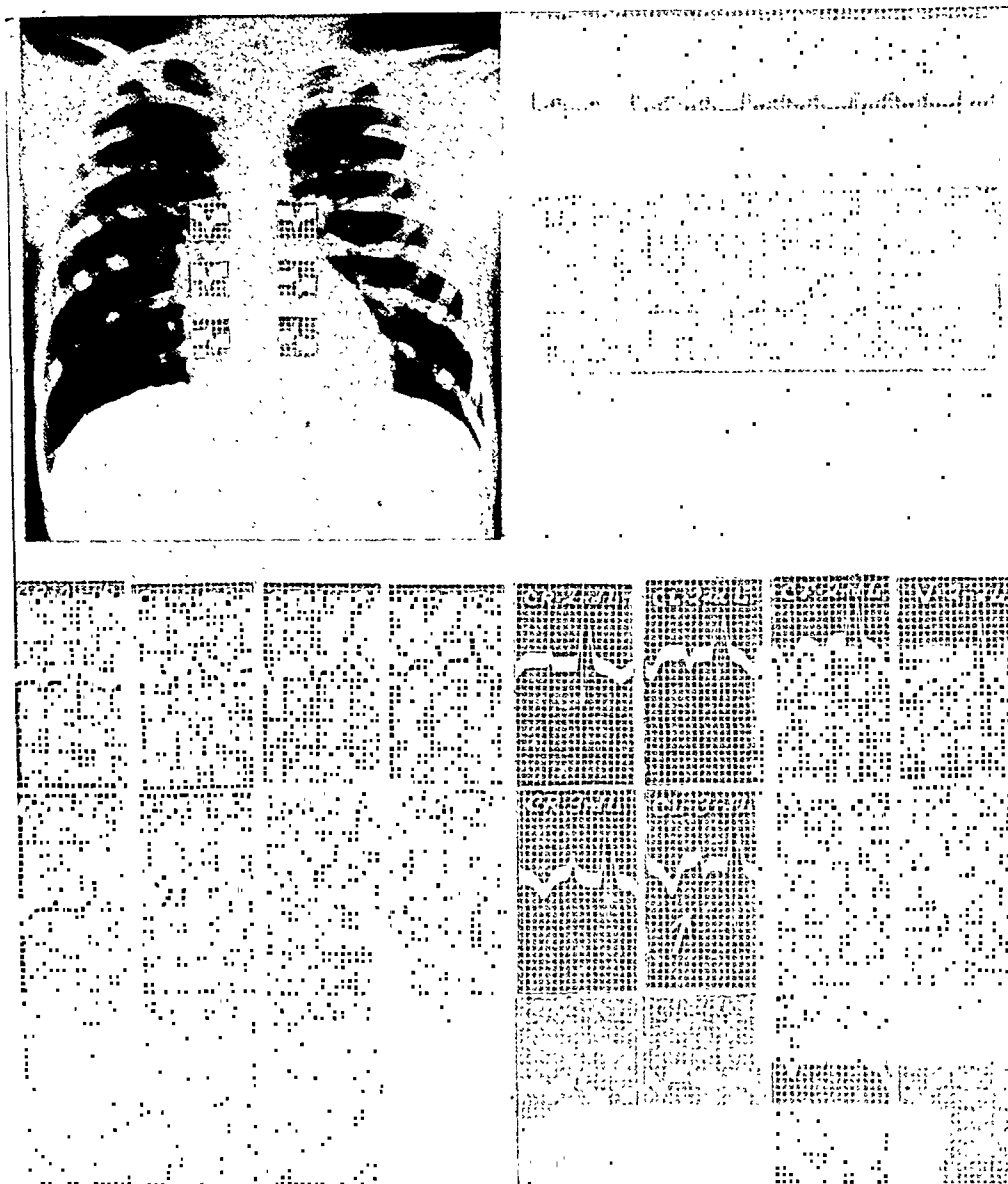


FIG. 3. Case III, chest film shows a moderate diffuse cardiac hypertrophy. Inserts are unipolar auricular electrograms taken from the positions indicated. Standard leads show large P wave in leads I and II. P-R measures 0.24 seconds. Moderate right axis deviation. Parasternal leads are taken from the second, third and fourth interspaces, right and left of sternum and paired with electrodes at the three extremities with a central terminal. Lettering is self-explanatory. Diphasic auricular waves with intrinsic deflections are seen in CL third left, unipolar third left, CL fourth right, unipolar fourth right and in CF third and fourth left.

it is proper to infer that the right auricle has undergone considerable enlargement, and that it lies close to the anterior chest wall to the left as well as to the right of the sternum.

CASE IV. Rheumatic carditis: D. F., a girl twelve years of age, had been a patient in Toledo Hospital during November and December, 1945, at which time she had an acute rheumatic pancarditis with involvement of the aortic

and mitral valves, relative tricuspid insufficiency and cardiac decompensation. Under rest and digitalis medication she had progressed favorably and was greatly improved when examined in March, 1946. The heart was much smaller, the signs of tricuspid insufficiency had disappeared, the liver was no longer palpable, and there was no peripheral edema. There was still present a mitral systolic murmur of moderate

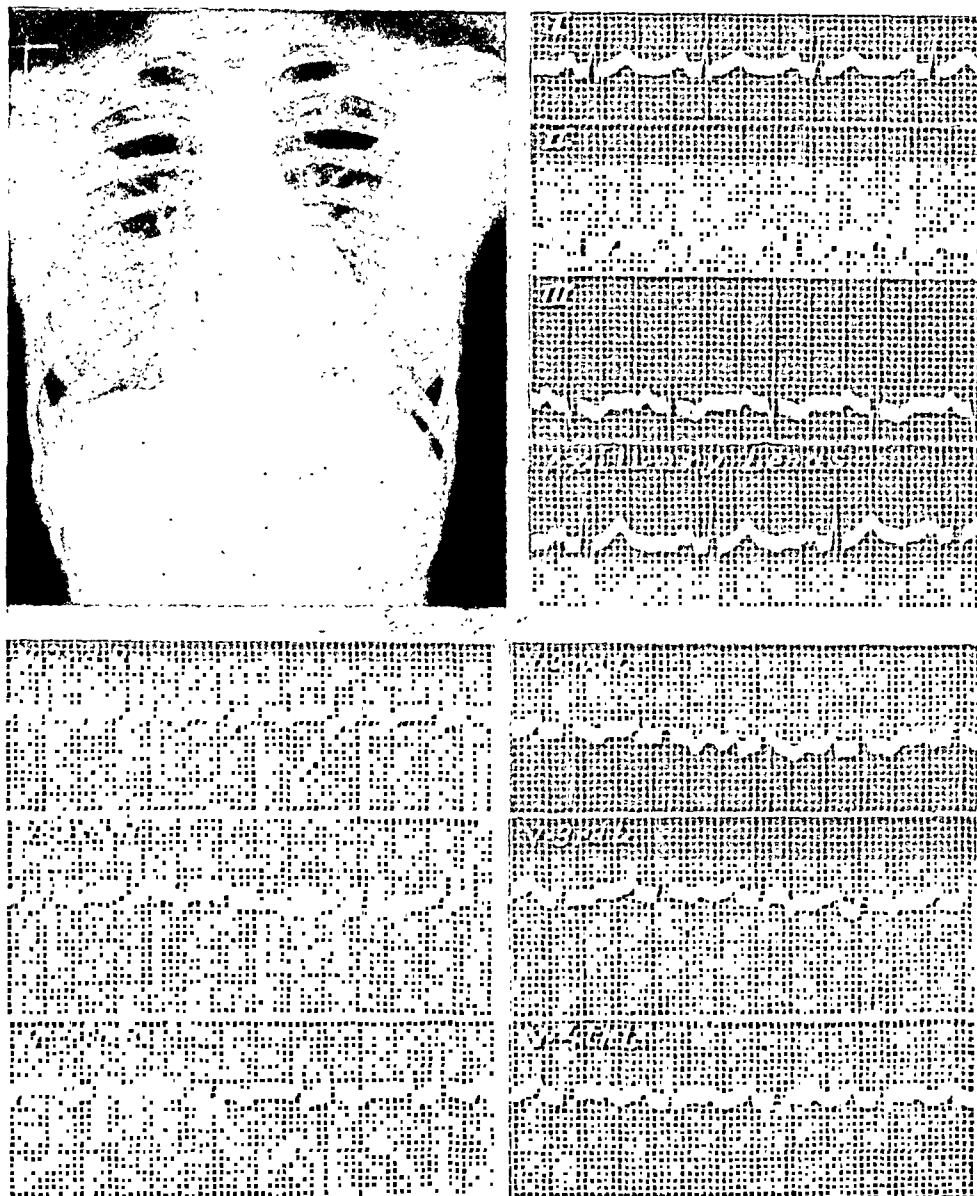


FIG. 4. Case iv, chest film shows a uniformly enlarged heart with a rounded pulmonary conus. The aortic knob is absent. Electrocardiogram shows right axis deviation, large P waves in leads I and II and broad, notched auricular waves in Whitten's axillary lead. The parasternal leads show diphasic auricular electrograms with intrinsic deflections in unipolar derivations from the interspaces to the right of the sternum.

intensity, but no diastolic murmur or presystolic thrill could be discovered.

The chest film (Fig. 4) shows a uniformly enlarged heart with considerable prominence of the pulmonary conus and a full rounded contour of the right cardiac border. The aortic knob is absent. The lung fields are clear. The electrocardiogram still shows a right axis deviation, but this is not as marked as in previous records. Conduction time, formerly increased, is now

normal. P waves are broad and notched; this deformity of the auricular complex is well illustrated in a Whitten lead taken from right and left axillary spaces. In this lead the P wave measures 0.12 sec. in duration and shows a definite bifurcation which may represent a block of Bachmann's interauricular bundle.<sup>1</sup>

Unipolar parasternal leads were taken from the second, third, and fourth interspaces to the right and left of the sternum. Large diphasic

auricular waves are found in all the right parasternal leads. They show the sharp fall of the intrinsic deflection characteristic of semidirect auricular electrograms and represent the position and size of the right auricle. It is interesting to note that the pre-intrinsic phase of the auricular complex becomes higher and sharper as the exploring electrode is moved downward on the chest. The downstroke of the intrinsic deflection occurs earlier at the higher levels where the exploring electrode is closer to the sino-auricular node. In electrograms taken during the height of the previous attack of rheumatic carditis, diphasic waves were also obtained in leads from the left of the sternum. The absence of such waves in this record clearly indicates a reduction in the size of the auricle and conforms to the clinical improvement and the absence of the signs of tricuspid regurgitation.

CASE V. Congenital heart: L. S., a bookkeeper twenty-six years of age, had been cyanotic since birth. There was no history of physical defects in the family. He escaped the usual diseases of childhood and had not suffered from respiratory infections. Deformities of the hands and feet were first noticed at the age of twelve. He has never been able to engage in work or recreation which required physical exertion because of a prohibitive shortness of breath.

He was examined in February, 1946, at which time he presented the classical symptoms of congenital heart disease of the Fallot type, with general cyanosis, dyspnoea on slight exertion, marked clubbing of fingers and toes and with soft tissue deformities about the ankles and wrists. There were no clinical signs of pulmonary complications. The heart was moderately enlarged and on palpation a double systolic impulse could be felt over the lower precordium. Auscultation revealed a loud systolic murmur, maximum in the fourth left interspace which was transmitted more clearly to the right than to the left. In the second left interspace a high pitched systolic murmur could be heard, but this was not accompanied by a thrill. The brachial pressure was 124/86 and the systolic pressure was 140 in the lower extremity by palpation.

Blood counts showed a compensatory poly-

cythemia with an erythrocyte count of 7,260,000 and a hemoglobin of over 140 per cent. The leukocyte count was 6,500 with a normal differential. X-rays of the extremities showed a broadening of the distal portion of the long bones, periosteal thickening and subperiosteal proliferation, especially noticeable in the lower third of the tibia and fibula. Roentgenograms of the chest showed the heart to have a modified *coeur-en-sabot* configuration with no fullness of the pulmonary conus. The right ventricle was conspicuous in the lateral film. Fluoroscopy showed an enlarged and somewhat displaced aorta and a synchronous pulsation in the aorta and in the right auricle. The diagnosis was tetralogy of Fallot with secondary hypertrophic osteoarthropathy.

Standard electrocardiograms showed a normal rhythm and right axis deviation. The auricular waves were tall and broad in leads I and II. Parasternal leads were taken from the second, third, and fourth right and left interspaces and were paired with an indifferent central terminal and also with the indifferent electrode in the interscapular area. Leads from the right interspace showed large diphasic P waves with an abrupt intrinsic deflection, characteristic of semidirect auricular electrograms. In this patient the diphasic waves appeared at a higher level than in other cases and this suggests an altered position of the heart as related to the location of the exploring electrodes. (Fig. 5.) The presence of these typical auricular electrograms indicates an enlargement of the right auricle and its displacement by the hypertrophied right ventricle.

The patient was operated by Dr. A. Blalock of Baltimore in May and an anastomosis established between the right common carotid and the right pulmonary arteries. Marked improvement followed this surgical procedure. Cyanosis almost disappeared, and the dyspnoea was greatly relieved. The blood count fell to 6,000,000 and the hemoglobin to 120 per cent. On June 20th electrocardiograms taken from the right parasternal spaces failed to show the characteristic diphasic waves which had been previously observed (Fig. 5). The change was taken to indicate a diminished strain on the

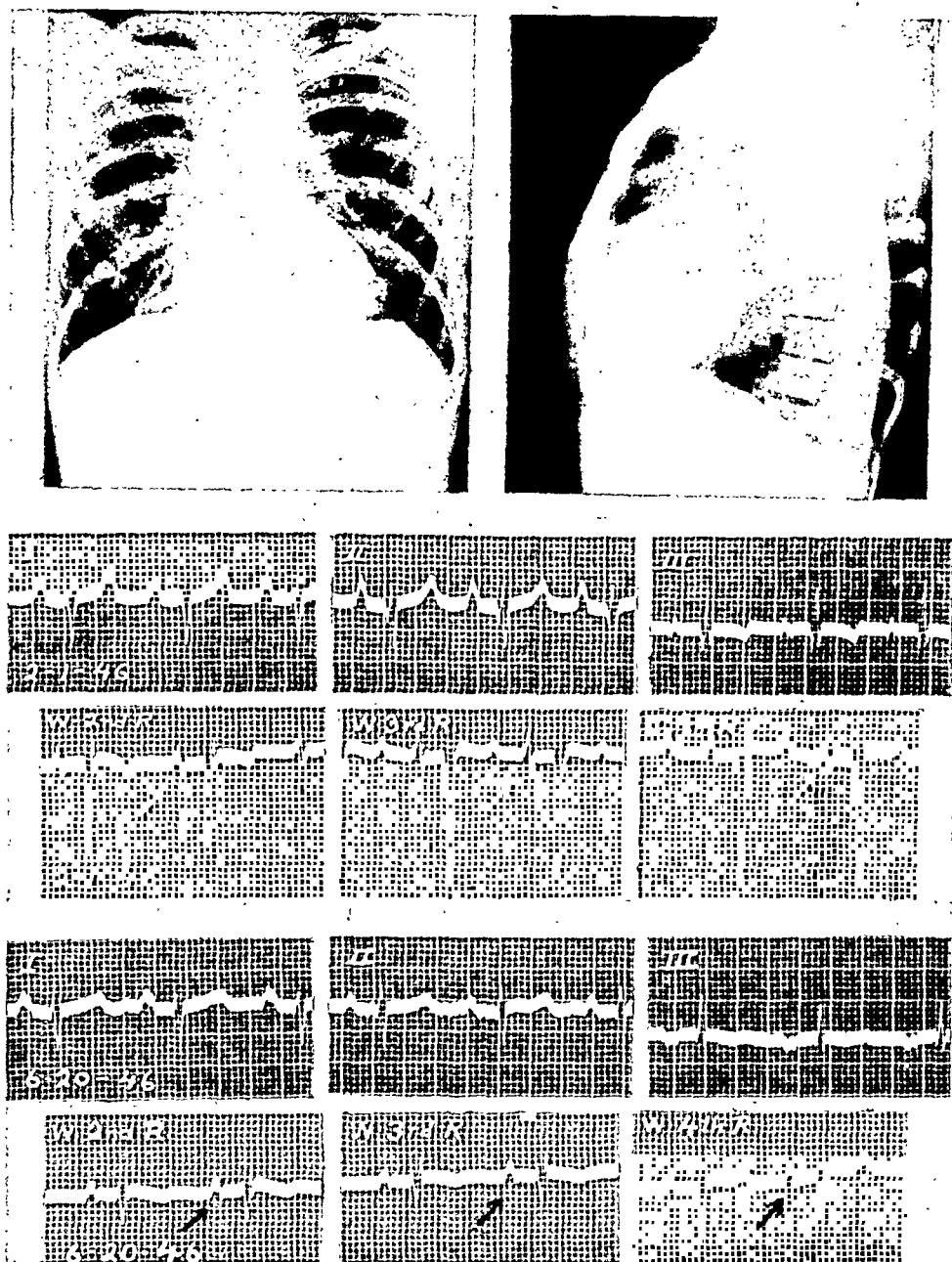


FIG. 5. Case v, frontal and lateral chest films in the tetralogy of Fallot, showing a modified coeur-en-sabot configuration with no convexity in the region of the pulmonary conus. Retrocardiac space is clear. The right ventricle presses against the anterior chest wall. The electrocardiogram shows a right axis deviation and large P waves in leads I and II. Parasternal leads paired with an electrode in the interscapular space show diphasic auricular waves with intrinsic deflections (white arrows). The lower electrocardiograms, taken seven weeks after a Blalock operation, show changes in the size and form of the T waves of standard leads. In the parasternal leads from the second, third and fourth right interspaces the auricular waves are now of the conventional type (black arrows) and no longer show the intrinsic deflection of the direct electrogram.

right auricle and a reduction in its size. Fluoroscopic examinations and oblique films confirmed this observation.

#### COMMENTS

In connection with our study of these semidirect leads it has been observed that in decompensation with right auricular enlargement diphasic waves were obtained from both right and left interspaces. As compensation was restored these waves were found only in leads from the right of the sternum.

It was also noted that when there was hypertrophy of both ventricles the right auricle was displaced to the right and downward, whereas when right ventricular hypertrophy was dominant the right auricle was displaced to the right or to the right and upward, as in Case v. When the right auricle itself was greatly enlarged intrinsic deflections were found in the auricular waves from the left as well as from the right interspaces.

When the character of the auricular complex returns to the conventional type and the intrinsic deflection can no longer be recorded in semidirect parasternal leads, it is evidence that the wall of the right auricle has receded to a degree which prevents the exploring electrode from receiving the potential variations of a semidirect electrogram. In Case II the diphasic waves disappeared from the parasternal leads within six months. In Case IV the intrinsic deflections disappeared from the left side of the sternum and at the time of the last observation could only be found in the right parasternal leads. In Case v, the tetralogy of Fallot, parasternal leads taken seven weeks after the carotid pulmonary artery anastomosis was established failed to reveal the diphasic auricular waves previously recorded. The change is illustrated in the electrocardiograms of Figure 5. Such observations on these and on other cases

where clinical improvement has occurred furnish convincing evidence that the finding of these diphasic auricular waves with the abrupt intrinsic deflection when present in parasternal leads, has a definite clinical significance and indicates an excessive strain on the right auricle.

#### SUMMARY

Parasternal leads using equipment ordinarily available yield satisfactory semidirect electrograms from the right auricle when it is under excessive strain. The use of a central terminal for the indifferent electrode was found to be more satisfactory than either the left leg or the right arm, as these locations exert a strong influence on the directional character of parasternal auricular deflections. Parasternal leads paired with electrodes on the left arm, in the interscapular space, or with a central terminal may be used interchangeably without altering the characteristic auricular deflections under discussion. By the presence and location of intrinsic auricular deflections information can be gained regarding the degree of enlargement and the position of the right auricle. Five selected cases showing the correlation of auricular electrograms with clinical and roentgenological findings are presented.

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# Investigations of the Cerebrospinal Fluid in Cases of Rheumatoid Arthritis<sup>\*</sup>

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**T**HE symptomatology of rheumatoid arthritis includes a large number of neurological symptoms which indicate that both the central and autonomic nervous systems are involved in this disease. This circumstance is particularly striking when the disease has a rapidly progressive course. In such cases a whole series of more or less pronounced neurological symptoms may be met with. For instance, pareses in the muscles of the extremities may be present which lead to difficulties in performing various movements. These pareses are especially striking either in the flexor muscles of the fingers, with the result that the hand can be only incompletely clenched actively or cannot be clenched at all; or in the extensor muscles of the fingers, with the result that the hand is in a clawlike position and the fingers cannot be straightened fully. In the early stage of the disease the fingers can be both flexed and straightened to the full extent passively, which shows that the obstacle to movement is not localized in the joints. Not until a later stage, when true joint symptoms have developed, is an arthrogenous mechanical obstacle to the performance of movements added. In association with the pareses, rapidly increasing muscular atrophy of the muscles of the extremities sets in (often to considerable degree before local joint symptoms have developed), accompanied by hydrops and thickening of the capsules and

therefore not the result only of inactivity. Along with these pareses, a pronounced coarse-waved tremor of an irregular type is met with in the fingers in these cases. Trophic disturbances in the form of local hyperhidrosis of the hand and feet, pigment changes in the skin on the dorsal surface of the hands and fingers, nail changes, atrophy of the skin and decalcification of the juxta-articular ends of the bones, which are so often encountered in more severe cases of arthritis, indicate that the vegetative nervous system has also been affected or is still involved.

As has been indicated, all the neurological symptoms mentioned may be present in severe, rapidly progressive cases of rheumatoid arthritis. Sometimes, however, one symptom or several symptoms predominate, while others are less pronounced or are absent altogether. In many, especially in the milder cases of chronic polyarthritis, neurological symptoms are not very prominent; but by careful examination, even in these cases, one or several of the symptoms indicated above can often be recognized.

In cases of rheumatoid arthritis in which clinical signs of involvement of both the central and autonomic nervous systems are found, it might reasonably be expected that indications of an affection of the central nervous system would also be detectable in the cerebrospinal fluid. No previous in-

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vestigations in this direction appear to have been made. In isolated cases increased protein values have been found in the spinal fluid in cases of rheumatoid arthritis. Thus, employing Mestrezat's diaphanometric method, Graber-Duvernay in 1939 found an increased protein content of the spinal fluid in eight of fifteen cases of rheumatoid arthritis. The method employed is now considered so unreliable that probably no positive conclusions can be drawn from Graber-Duvernay's investigations. In 1942, Sundelin published thirty-four cases of rheumatoid arthritis in which the spinal fluid had been examined by the Izikowitz method. In thirteen of the cases (38 per cent), clearly pathological protein values were obtained, in that the total protein was significantly elevated in five cases, the globulin content in six cases, the albumin content in three cases and the globulin-albumin quotient raised in eight cases and lowered in one case. Ludwig, Short and Bauer, 1943, examined cerebrospinal fluids from, *inter alia*, fifty-nine cases of rheumatoid arthritis and found increased protein values in four cases (6.8 per cent) and pathological colloidal gold curves in five cases (8.5 per cent). The analytical method employed by the authors was Denis-Ayer's nephelometric procedure which, according to Izikowitz (1941), is reliable on the whole but is impaired by chance deviations of considerable magnitude (standard deviation =  $10.50 \pm 0.74$  mg. per cent).

A clinically serviceable and sufficiently exact method of determining both the total protein and the albumin and globulin fractions in the spinal fluid was described by Izikowitz in 1941. The normal values for the protein content and its various fractions found by Izikowitz were re-investigated by Wiberg (1943), Rune Olsson (1944) and Eeg-Olofson (1944), the results showing good agreement with the

Izikowitz values. As to the method, reference should be made to Izikowitz's work.

Since 1940, I have examined the spinal fluid in 141 cases of rheumatoid arthritis: thirty-eight men and one hundred and three women. The cases in question were not selected in any way, except insofar as only clinically certain cases of rheumatoid arthritis were included. Three of the male cases also exhibited ankylopoietic spondylarthritis. With regard to the degree of severity of the disease in these patients, seventeen may be classified as mild, fifty-five as moderately severe and sixty-nine as severe cases. The duration of the disease before examination varied between four months and twenty years. By far the greater number of cases, however, had been affected between one and one-half and three years. When the examination was made, all the cases but two were afebrile. The two febrile cases had temperatures of  $38^{\circ}\text{C}$ .

The specimens were taken by lumbar puncture between  $L_4$  and  $L_5$  with the patient in a recumbent position. About 12 cc. was drawn off and this amount of fluid was immediately divided up into different portions for examination of the cell content, qualitative protein investigation according to Nonne-Apelt and Pandey, colloidal gold-sol reaction, Meinicke's  $\pi$  reaction and quantitative determination of the total protein, albumin and globulin by the Izikowitz method. The quantitative protein determinations were made by Dr. Izikowitz in his laboratory. This investigator was unaware of the clinical diagnosis of the cases from which the spinal fluids had been taken. In addition to chronic rheumatoid arthritis cases, parallel cases of chronic neurological diseases and prolapse of the nucleus pulposus were subjected to similar examination of the fluid with no diagnosis indicated.

The investigations of the spinal fluids

were made before any treatment of the patients had been initiated. In sixty-three cases the patients had previously received gold treatment, as a rule several months or years earlier. In twelve of these cases gold treatment had been discontinued as recently as two to four months before the investigation. In all the cases Meinicke's II reaction was negative.

Of the 141 cases investigated, 58 (41 per cent) exhibited protein values pathological in one way or another, and some of these cases also showed pathological gold-sol curves. (Table IA, IB.) In seven cases with normal protein values the gold-sol reaction was pathological. In six of the cases with raised protein values the cell content of the fluid was increased (4 or more cells per mm.<sup>3</sup>) at the same time. In only one case with a pathological cell increase (7.5 leukocytes and 5.5 lymphocytes per mm.<sup>3</sup>.) were all the protein values normal. Thus a total of 66 cases (46.8 per cent) exhibited spinal fluids which were pathologically changed in one way or another.

TABLE IA

CASES OF RHEUMATOID ARTHRITIS WITH INCREASED PROTEIN CONCENTRATION OR GLOBULIN-ALBUMIN QUOTIENT IN THE SPINAL FLUID (MALE PATIENTS)

Case No.	Age	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globulin-Albumin Quotient	Cells per 3.2 Mm. <sup>3</sup>	Gold-sol Reaction
3	38	62.97	14.21	48.76	0.29	4.16	
5	45	57.63	21.04	36.59	0.57	60.80	
6	50	25.50	7.90	17.60	0.45	1.92	
12	31	30.01	10.64	19.37	0.55	2.88	0011100000
14	25	37.65	13.23	24.42	0.54	1.92	0123311000
17	33	28.57	7.65	20.92	0.37	3.84	0122100000
19	53	36.45	14.20	22.25	0.64	47.04	0000000000
24	35	30.16	9.71	20.45	0.47	0.96	1111111110
28	49	29.27	7.77	21.50	0.36	10.56	
29	57	27.86	8.73	19.13	0.46	2.88	1222111000
30	23	39.06	15.69	23.37	0.67	5.44	1110000000
31	53	53.98	20.37	33.61	0.61	0	1111111110
32	46	53.05	10.71	42.34	0.25	47.60	
34	28	24.92	6.62	18.30	0.36	2.88	1233335333
35	45	18.69	6.50	12.19	0.53	0	1111000000
36	15	35.00	9.98	25.02	0.40	0	0111111000

Of the fifty-eight cases with pathological protein values, fifteen were men and forty-three women.

TABLE IB

CASES OF RHEUMATOID ARTHRITIS WITH INCREASED PROTEIN CONCENTRATION OR GLOBULIN-ALBUMIN QUOTIENT IN THE SPINAL FLUID (FEMALE PATIENTS)

Case No.	Age	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globulin-Albumin Quotient	Cells per 3.2 Mm. <sup>3</sup>	Gold-sol Reaction
41	19	20.07	5.38	19.69	0.37	5.12	
49	11	21.70	6.94	14.76	0.47	0	
51	36	51.42	10.29	41.13	0.25	1.92	0044330000
52	46	63.45	27.63	35.82	0.77	12.80	0116666200
53	38	20.27	5.35	14.92	0.36	4.48	
56	15	65.08	21.95	43.13	0.51	3.20	
57	31	30.28	8.62	21.66	0.40	3.20	0011110000
59	43	27.94	9.58	18.36	0.52	4.80	1111111000
60	38	45.17	11.93	33.24	0.36	16.00	
69	22	47.62	8.69	38.93	0.22	2.88	0012221000
71	38	67.23	21.04	46.19	0.46	22.40	1122221000
72	22	56.16	12.51	43.65	0.29	9.28	1123211110
74	37	39.95	11.86	28.09	0.42	0.96	1332170000
75	35	24.28	8.67	15.61	0.56	0	0000000000
77	52	26.53	7.84	18.69	0.42	2.88	1111122111
81	23	26.32	7.14	19.18	0.37	2.88	0111100000
86	33	45.32	13.37	32.01	0.42	0.96	0111100000
87	40	32.66	9.73	22.93	0.42	0	1122221100
89	33	23.34	7.94	15.40	0.52	3.20	1111111000
93	38	50.89	11.98	38.91	0.31	3.20	1122111000
97	54	32.28	9.37	22.91	0.41	12.80	0111100000
99	50	35.37	19.28	16.09	1.20	0	0122110000
102	23	60.27	5.06	11.21	0.45	1.92	
103	40	27.44	8.32	19.12	0.44	0.96	1111110000
104	46	27.42	8.83	18.59	0.47	1.92	2221111100
105	41	31.09	8.46	22.63	0.37	2.88	
106	40	26.91	8.03	18.88	0.43	0	
107	34	21.63	6.33	14.90	0.42	2.88	1111100000
109	46	39.76	11.15	28.61	0.39	1.92	
111	28	41.56	20.50	21.06	0.97	0.96	1111100000
112	38	27.74	9.09	18.65	0.49	1.92	1111100000
113	54	23.96	6.62	17.34	0.38	1.92	1224444444
114	18	24.00	6.41	17.59	0.36	3.84	1111110000
116	19	20.34	5.64	14.70	0.38	0.96	1111111000
117	28	19.71	5.79	13.92	0.42	0.96	1111000000
119	37	27.74	7.71	20.03	0.38	1.92	0000000000
121	53	42.41	12.29	30.12	0.41	1.92	1111111111
126	53	43.93	11.44	32.49	0.35	2.88	1111110000
127	17	21.64	7.04	14.60	0.48	7.04	1111100000
133	19	19.90	7.69	12.21	0.63	0.96	1122222232
138	53	28.50	7.50	21.00	0.36	0.96	1111100000
140	29	18.21	6.30	11.91	0.53	1.92	1121110000
141	17	27.73	8.21	19.52	0.42	0.96	1221100000

The total protein was above normal limits in six cases, all women, the values varying between 51 and 67 mg. per cent. According to Izikowitz, the mean value for the total protein of the spinal fluid in normal women is 31 mg. per cent and the maximum "permissible" statistically calculated normal value is 48.7 mg. per cent.

The globulin content exceeded normal limits in seventeen cases, five of which were men and twelve were women. The values for the men varied between 14 and 21 mg. per cent, as against a mean value of 7.7 mg.

per cent and a maximum “permissible” value of 13.7 mg. per cent for normal males. The values for the women were between 11 and 28 mg. per cent, as against the mean value of 6 mg. per cent and the maximum “permissible” value of 10.7 mg. per cent in normal females.

The albumin content was increased in six cases, all women, and varied between 38.91 mg. per cent and 46.19 mg. per cent; as against the mean value of 22.9 mg. per cent and the maximum “permissible” value of 38.39 mg. per cent in normal persons.

The globulin-albumin quotient proved to be abnormally high in fifty-two cases, fourteen of which were men and thirty-eight women. In the men the elevated quotient was between 0.36 and 0.67, as against a mean value of 0.24 and a maximum “permissible” value of 0.34 in normal males. In the women the elevated quotient was between 0.36 and 1.20, as against a mean value in normal females of 0.25 and a maximum “permissible” value of 0.36.

Of the three patients who had ankylopoietic spondylarthritis simultaneously with rheumatoid arthritis, two had completely normal protein values in the spinal fluid, while the third had a raised globulin-albumin quotient of 0.36.

A summary of the various combinations of pathologically increased protein values is given in Table II.

A statistical study of the material with regard to total protein, the different protein fractions and the globulin-albumin quotient showed (Table III), *inter alia*, no significant difference between the values found for men and women. In respect to the total protein value, however, a larger material would probably show that the total protein is higher in men than in women, i.e., in agreement with the findings in healthy persons. No difference between the sexes could be established with regard to the globulin-albumin quotient; which

would imply that both globulin and albumin values are higher in men than in women. Thus, to sum up, it could be established that in these arthritic cases there was approximately the same difference between the sexes with respect to total protein, globulin and albumin values as is found in normal subjects.

TABLE II  
PATHOLOGICALLY INCREASED PROTEIN VALUES  
IN THE SPINAL FLUID

Increase in	Men	Women
Quotient only.....	10	29
Globulin only.....	1	1
Albumin only.....	..	1
Globulin, quotient.....	4	6
Total protein, albumin.....	..	1
Total protein, globulin, albumin.....	..	2
Total protein, globulin, quotient.....	..	1
Total protein, globulin, albumin, quotient.....	..	2
Total.....	15	43

If a comparison is made between the protein values obtained and the normal values found in a large series by Izikowitz, no considerable difference appears in the total protein values. On the other hand, it is certain that in cases of rheumatoid arthritis the globulin value is increased, the albumin value lowered and the quotient considerably elevated. The mean value for the globulin-albumin value found here is 0.36 as compared with 0.25 normally.

Since the globulin content of the spinal fluid proved to be elevated in cases of rheumatoid arthritis, it was of interest to investigate the colloidal gold reaction. Kabat, Landow and Moore (1942) showed that in a number of diseases the colloidal gold reaction was conditioned entirely by gamma globulin and not by the albumin fraction, but it was pointed out at the same time that the gamma globulin, which in these cases affects the gold-sol reaction, must in some way be different from that

TABLE III

PROTEIN VALUES (MG PER CENT) AND GLOBULIN/ALBUMIN QUOTIENT IN THE SPINAL FLUID IN CASES OF RHEUMATOID ARTHRITIS

	Men			Women			Difference D $\pm$ $\Sigma$ (D)
	No.	M $\pm$ $\Sigma$ (M)	$\sigma$	No.	M $\pm$ $\Sigma$ (M)	$\sigma$	
Total protein.....	38	36.3 $\pm$ 1.8	11.0	103	30.9 $\pm$ 1.0	10.1	5.4 $\pm$ 2.0
Globulin.....	38	9.3 $\pm$ 0.6	3.9	103	8.0 $\pm$ 0.4	3.9	1.3 $\pm$ 0.7
Albumin.....	38	27.0 $\pm$ 1.4	8.5	103	22.9 $\pm$ 0.7	7.5	4.1 $\pm$ 1.6
Globulin-albumin quotient.....	38	0.36 $\pm$ 0.021	0.13	103	0.36 $\pm$ 0.014	0.14	0.0 $\pm$ 0.025

normally found in the spinal fluid, since normal spinal fluid does not give a pathological gold curve.

In this material the gold-sol reaction was investigated in 107 cases, twenty-seven of which were men and eighty women.\* In fifteen cases, three men and twelve women, i.e., in 14 per cent of the cases investigated, the gold-sol reaction gave a positive (pathological) result. In eight cases, thus in somewhat more than half, the pathological gold-sol reaction was obtained in cases that had protein values which were abnormal in one way or another. In the other seven cases the protein reaction in the spinal fluid was within normal limits. Closer scrutiny of the cases which had abnormal gold-sol reactions and at the same time elevated protein values reveals (Table I) that all but one had an absolute or relative increase in the globulin content of the spinal fluid. But as the gold-sol reaction was normal in 76 per cent of the patients who had increased spinal fluid protein values, and furthermore was positive in a number of cases with normal protein values, it is manifest that the positive reaction in some cases could not be conditioned only by a quantitative increase in globulin values. Thus it is clear that in rheumatoid arthritis there must exist some other, hitherto un-

known, factor which in certain cases results in a pathological gold-sol curve.

It is now of interest to determine whether the degree of severity of rheumatoid arthritis had any connection with the pathologically increased protein values in the spinal fluid. The grouping of our material in respect to severity of disease must naturally be somewhat schematic. Consideration was paid to the general course of the disease: whether it exhibited a rapid progression; whether multiple, few, or single joints were involved; and whether the joint symptoms were severe or slight. On this basis the material was divided into three groups: mild, moderately severe and severe cases. The number of cases falling into each group has already been stated and this is also shown in Tables IVa and IVb.

From Table IVa it is evident that, on the whole, the protein and quotient values are

TABLE IVa  
PROTEIN VALUES IN THE SPINAL FLUID IN VARYING DEGREES OF SEVERITY OF THE ARTHRITIC DISEASE PROCESS

Degree of Severity	No. of Cases	Total Protein	Globulin	Albumin	Quotient
<i>Men</i>					
I	8	36.8	8.5	28.3	0.32
II	14	32.7 $\pm$ 2.8	8.3 $\pm$ 1.0	24.3 $\pm$ 2.1	0.35 $\pm$ 0.030
III	16	39.2 $\pm$ 3.0	10.6 $\pm$ 1.1	28.6 $\pm$ 2.4	0.38 $\pm$ 0.038
<i>Women</i>					
I	9	34.6	8.0	26.6	0.31
II	41	31.3 $\pm$ 1.7	7.8 $\pm$ 0.6	23.5 $\pm$ 1.3	0.34 $\pm$ 0.020
III	53	29.9 $\pm$ 1.3	8.1 $\pm$ 0.6	21.8 $\pm$ 0.8	0.38 $\pm$ 0.022

\* The gold-sol reaction was not carried out in all the cases because of a shortage of the necessary reagent during certain periods of the war years.

TABLE IVB  
DISTRIBUTION OF SPINAL FLUID PROTEIN VALUES ACCORDING  
TO THE DEGREE OF SEVERITY OF THE ARTHRITIC  
DISEASE

Protein Value		Degree of Severity			
		I	II	III	Total
<i>Men</i>					
Pathological value	{No...	2	5	8	15
	{%...	13.3	33.3	53.4	100.0
Normal value	{No...	6	9	8	23
	{%...	26.1	39.1	34.8	100.0
<i>Women</i>					
Pathological value	{No...	5	16	22	43
	{%...	11.6	37.2	51.2	100.0
Normal value	{No...	4	25	31	60
	{%...	6.7	41.7	51.6	100.0
<i>Both sexes</i>					
Pathological value	{No...	7	21	30	58
	{%...	12.1	36.2	51.7	100.0
Normal value	{No...	10	34	39	83
	{%...	12.0	41.0	47.0	100.0

similar in the three groups and that the degree of severity of the disease does not appear to affect the protein values. If the cases with pathological and normal protein values are considered according to the degree of severity of the disease process (Table IVB) it is found that the distribution is the same irrespective of whether or not the cases exhibit abnormal spinal fluid values.

The degree of severity of the disease is also reflected by the erythrocyte sedimentation rate (S.R.). If the sedimentation rate in the different cases (Table V) is scrutinized, it is found that no considerable differences can be established between cases with pathological and those with normal protein contents of the cerebrospinal fluid.

Another factor which may conceivably affect the protein content of the cerebrospinal fluid is the duration of illness. The material has therefore been divided up into cases dating back at most one year and cases with a duration of more than one year. (Table VIA.) The analysis shows that duration of illness does not appear to have

TABLE V  
THE ERYTHROCYTE SEDIMENTATION RATE IN PATIENTS WITH  
PATHOLOGICAL AND NORMAL PROTEIN VALUES  
IN THE SPINAL FLUID

Spinal Fluid Protein Value	No. of Cases	Mm./One Hr.	Mm./Two Hr.
<i>Men</i>			
Pathological.....	15	55 ± 8	89 ± 7
Normal.....	23	42 ± 6	72 ± 7
<i>Women</i>			
Pathological.....	43	57 ± 5	83 ± 5
Normal.....	60	51 ± 4	80 ± 4

any connection with the protein content of the cerebrospinal fluid. On the other hand, if the duration of illness in cases with abnormally elevated spinal fluid protein values and in those with normal protein values is considered (Table VIB), it is found that, in general, cases with pathological protein values appear to be of shorter duration.

As a number of the arthritic cases investigated had previously received gold treatment for months or even years, and as this might conceivably have affected the protein in the spinal fluid, this circumstance has received special attention. It appears, however, that no significant difference in values was obtained in patients who were treated and those who were not treated with gold. (Table VII.)

As has been mentioned previously, Nonne-Apelt's and Pandy's protein reactions were carried out parallel with the quantitative protein determinations. Izikowitz (1941), later Gripwall (1943) and Wiberg (1943) have shown that there is a considerable discrepancy between the results of the Nonne-Apelt and the Pandy reactions, and the concentrations of total protein and globulin in the spinal fluid. In the present arthritis series, too, very unsatisfactory agreement was found between the quantitative total protein values obtained and the qualitative protein reactions (Table VIII). Of the cases with pathological values in the spinal fluid (both sexes) only 7 per cent

TABLE VIA

SPINAL FLUID PROTEIN VALUES IN VARYING DURATION OF ILLNESS IN ARTHRITIS

Duration of Illness	No. of Cases	Total Protein	Globulin	Albumin	Quotient
<i>Men</i>					
Less than 1 year.....	18	39.6 ± 2.7	10.4 ± 0.8	29.2 ± 2.2	0.37 ± 0.031
More than 1 year.....	19	33.6 ± 2.3	8.4 ± 0.9	25.2 ± 1.7	0.34 ± 0.030
<i>Women</i>					
Less than 1 year.....	26	28.4 ± 1.6	6.9 ± 0.4	21.5 ± 1.4	0.34 ± 0.015
More than 1 year.....	77	31.7 ± 1.2	8.3 ± 0.5	23.4 ± 0.9	0.36 ± 0.018

exhibit a positive Nonne and 11 per cent a positive Pandy reaction. Even if doubtful reactions are added, not more than 27 per cent of positive Nonne and 34 per cent of positive Pandy reactions are included. Furthermore, it is evident that among the cases with protein values within normal limits, there is as large a percentage of positive or doubtful Nonne and Pandy reactions as there is among cases with pathological spinal fluid protein levels.

If the protein values for the seven cases which exhibited positive cell findings in the spinal fluid are examined (Table IXA), it is found that in one case all the protein values were normal; in one case the quotient was abnormally high; in three cases the

TABLE VIB  
AVERAGE DURATION OF ILLNESS IN PERSONS WITH  
RHEUMATOID ARTHRITIS GROUPED ACCORDING TO  
PATHOLOGICAL OR NORMAL PROTEIN VALUES  
IN THE SPINAL FLUID

Protein Value	No. of Cases	Duration of Illness (Years)	
		Average	Median
<i>Men</i>			
Pathological.....	14	$1.0 \pm 0.16$	1
Normal.....	23	$3.3 \pm 0.78$	2
<i>Women</i>			
Pathological.....	43	$3.5 \pm 0.50$	2
Normal.....	60	$4.2 \pm 0.54$	3
<i>Both sexes</i>			
Pathological.....	57	$2.9 \pm 0.4$	1.5
Normal.....	83	$3.9 \pm 0.4$	3

TABLE VIII  
THE NONNE-APELT AND PANDY PROTEIN REACTIONS IN  
PATIENTS WITH PATHOLOGICAL AND NORMAL PROTEIN  
CONTENTS OF THE SPINAL FLUID

Protein Value	Positive	Doubtful	Negative	Total
Nonne				
<i>Men</i>				
Pathological { No.....	2	6	6	14
{ %.....	14.2	42.9	42.9	100.0
Normal { No.....	2	9	12	23
{ %.....	8.7	39.1	52.2	100.0
<i>Women</i>				
Pathological { No.....	2	5	35	42
{ %.....	4.8	11.9	83.3	100.0
Normal { No.....	1	13	45	59
{ %.....	1.7	22.0	76.3	100.0
<i>Both sexes</i>				
Pathological { No.....	4	11	41	56
{ %.....	7.1	19.6	73.2	100.0
Normal { No.....	3	22	57	82
{ %.....	3.7	26.8	69.5	100.0
Pandy				
<i>Men</i>				
Pathological { No.....	2	5	7	14
{ %.....	14.2	35.8	50.0	100.0
Normal { No.....	3	8	11	22
{ %.....	13.6	36.4	50.0	100.0
<i>Women</i>				
Pathological { No.....	4	8	30	42
{ %.....	9.5	19.0	71.5	100.0
Normal { No.....	1	17	41	59
{ %.....	1.7	28.8	69.5	100.0
<i>Both sexes</i>				
Pathological { No.....	6	13	37	56
{ %.....	10.7	23.2	66.1	100.0
Normal { No.....	4	25	52	81
{ %.....	4.9	30.8	64.3	100.0

globulin and quotient were elevated; in one case the total protein, globulin and

TABLE VII

SPINAL FLUID PROTEIN VALUES IN CASES OF ARTHRITIS TREATED OR NOT TREATED WITH GOLD

Group	No. of Cases	Total Protein	Globulin	Albumin	Globulin-Albu- min Quotient
<i>Men</i>					
Treated with gold.....	15	34.0 ± 2.8	8.9 ± 1.1	25.1 ± 2.1	0.36 ± 0.033
Not treated with gold.....	23	37.8 ± 2.3	9.6 ± 0.5	28.2 ± 1.8	0.36 ± 0.028
<i>Women</i>					
Treated with gold.....	48	30.9 ± 1.4	8.0 ± 0.5	22.9 ± 1.0	0.36 ± 0.023
Not treated with gold.....	55	30.8 ± 1.4	7.9 ± 0.6	22.9 ± 1.0	0.35 ± 0.017

quotient were pathologically increased and in one case the total protein, globulin, albumin and quotient were all abnormally high.

TABLE IXA  
SPINAL FLUID PROTEIN VALUES IN PATIENTS WITH INCREASED NUMBER OF CELLS IN THE SPINAL FLUID

Case Number	Cells per 3.2 Mm. <sup>3</sup>	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globu- lin-Al- bumin Quotient
32 ♂	41.6	53.05	10.71	42.34	0.25
97 ♀	12.8	32.28	9.37	22.91	0.41
19 ♂	47.04	36.45	14.20	22.25	0.64
5 ♂	60.8	57.63	21.04	36.59	0.57
60 ♀	16.0	45.17	11.93	33.24	0.36
52 ♀	12.8	63.45	27.63	35.82	0.77
71 ♀	22.4	67.23	21.04	46.19	0.46

If the whole material is scrutinized with respect to protein content and cell findings in the spinal fluid (Table IXB) the frequency of increased cell counts seems to be somewhat greater in cases with increased protein contents. The material is not sufficiently large, however, to afford definite data in this respect.

Finally, an inquiry was also made as to whether the patients with rheumatoid arthritis who exhibited pathologically raised protein values in the spinal fluid had any clinically overt neurological symptoms. It was found, first, (Table x) that some cases exhibited a pronounced tremor of the

fingers and hands of a peculiar type, which can best be characterized as a combination of a relatively short-wave tremor (which is both visible and palpable) and a more irregular athetotic coarse-wave tremor. A tremor of this kind was observed in about half the cases with increased protein values in the spinal fluid.

TABLE IXB  
DISTRIBUTION OF INCREASED CELL COUNTS IN THE SPINAL FLUID OF PATIENTS WITH ELEVATED AND NORMAL SPINAL FLUID PROTEIN VALUES

Protein Value	No. of Cases	No. of Cases With At Least 4 Cells (Leukocytes and Lymphocytes) in the Spinal Fluid Count	
		No.	
Pathological.....	58	6	10.3 ± 4.0
Normal.....	83	1	1.2 ± 1.2
			Diff. 9.1 ± 4.17

TABLE X  
NEUROLOGICAL SYMPTOMS IN FIFTY-EIGHT CASES OF RHEUMATOID ARTHRITIS WITH INCREASED PROTEIN VALUES IN THE SPINAL FLUID

Symptom	Men	Women	Total
Tremor.....	10	18	28
Paresis.....	13	38	51
Muscular atrophy.....	12	35	47
Vegetative disturbances.....	12	19	31
Miscellaneous.....	2	7	9

Another symptom frequently met with was an appreciable paretic impairment of function of the hands and fingers. This showed itself in an incapacity either to clench the fists entirely, or, if that could be

done, in a markedly weakened hand clasp. Obviously, local changes in the joints, in the form of swelling of the joint capsules, hydrops and pain, may impede or prevent the clenching of the hand, but such cases have not been regarded as paretic. Only in those patients who exhibited reduced power of movement in the hands with joint symptoms of subordinate importance was paresis of the flexors of the fingers (or in some cases the extensors of the fingers) considered to be present. Such pareses of the fingers were present in fifty-two of the fifty-eight cases with abnormally elevated spinal fluid protein.

Visible atrophy of the interosseous muscles was also met with in a large number of cases, specifically in forty-seven of the fifty-eight with pathological spinal fluids.

Vegetative disturbances in the form of abnormal sweating, marked cyanosis or edematous swelling of the skin of the hands, pigment changes in the skin and nail changes (including one patient with skin changes resembling scleroderma in the fingers) were encountered in thirty-one cases of the fifty-eight in this series.

General muscular atrophy or muscular atrophy localized to single large joints was observed in nine cases.

As regards neurological manifestations in cases of rheumatoid arthritis, it may be said by way of summary that all except one of the cases with a pathologically increased protein content in the spinal fluid exhibited one or more neurological symptoms. An analysis of the number of such symptoms gives the following figures:

No neurological symptoms . . . . .	1 woman
One neurological symptom . . . . .	2 men and 4 women
Two neurological symptoms . . . . .	2 men and 11 women
Three neurological symptoms . . . . .	2 men and 19 women
Four neurological symptoms . . . . .	9 men and 8 women

The above mentioned neurological symptoms were also met with in about the same proportions in the cases of rheumatoid arth-

ritis with normal protein values in the spinal fluid at the time of the examination.

#### SUMMARY

The spinal fluid was examined in 141 cases of rheumatoid arthritis, thirty-eight men and 103 women, of whom fifty-eight (41 per cent) exhibited a protein content that was pathological in one way or other, fifteen (14 per cent) gave a pathological gold-sol reaction and seven showed an increased spinal fluid cell count. Altogether sixty-six cases (46.8 per cent) were found to have spinal fluids which were pathologically altered in some way.

Statistical examination of the results shows, *inter alia*, that in cases of rheumatoid arthritis the average spinal fluid globulin value is increased and the average spinal fluid albumin value lowered, resulting in a raised average globulin-albumin quotient. Further, it was shown that the abnormal increases in spinal fluid protein values are not dependent on the degree of severity of the arthritic disease process and are little affected by the duration of the disease.

The frequency of increased cell counts in the spinal fluid appears to be somewhat greater in cases with elevated protein contents.

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# Sulfadiazine Sensitivity with Demonstrable Skin-sensitizing Antibody in the Serum\*

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SINCE Prausnitz and Küstner in 1921<sup>1</sup> described the phenomenon of passive transfer and established the skin-sensitizing antibody as the basis of a large group of allergic reactions, the possibility of demonstrating such antibodies in cases of idiosyncrasy to drugs of simple chemical structure has interested both clinicians as a diagnostic method and immunologists as evidence of the chemical nature of antigens. In 1926, Biberstein<sup>2</sup> reported passive transfer of sensitivities to mercury salts, salvarsan, bismuth and pyramidon, and a few other similar reports have appeared in foreign literature.<sup>3</sup> However, numerous attempts by researchers in this country to reproduce these same results have failed and for years the existence of transferable antibodies for drugs of simple structure was doubted by most authorities in this country,<sup>4,5</sup> although Kern<sup>6</sup> in 1938 did describe a case of rhinitis and bronchial asthma due to phthalic anhydride (a simple, nitrogen-free compound), with an immediate urticarial reaction to scratch test and a typical passive transfer reaction to this substance. More recently, Feinberg and Watrous<sup>7</sup> reported similar cases of asthma and rhinitis in workers exposed to halazone and chloramine T, both simple synthetic drugs, also showing typical urticarial reactions by direct scratch tests and on passive transfers.

Soon after the introduction of the sulfonamide drugs, numerous cases of acquired

sensitivity to these compounds were reported. The usual story was that the patient tolerated the first course of the drug without symptoms, or, if the first course was prolonged, developed fever or a skin rash or both, only after receiving the drug for seven to ten days. However, when the drug was administered a second time weeks or months later, the skin rash or fever appeared within a few hours after the first dose.<sup>8</sup> In many instances, the existence and specificity of the sensitivity were proven clinically by intentionally repeating small doses of the causative and related drugs,<sup>9-14</sup> but attempts to confirm the diagnosis by skin tests were usually unsuccessful. In a few patients with drug rashes positive patch tests were obtained<sup>15,16,17</sup> but scratch and intracutaneous tests with the drugs were uniformly negative.<sup>13,18-23</sup> Leftwich<sup>23</sup> reported positive reactions when the sensitive patients were tested intracutaneously with serums of persons who were taking the causative drugs, but other authors had negative results with similar drugs<sup>22</sup> as well as with normal human serum to which the drugs had been added.<sup>24</sup> In a few instances, skin tests were made with diazotized sulfonamides coupled to normal human serum, but the results were again negative.<sup>9,25</sup>

Likewise, attempts to demonstrate antibodies in the serums of sulfonamide-sensitive patients by precipitin tests<sup>9,18</sup> and by passive sensitization of guinea pigs gave negative results.<sup>9,18</sup> Passive transfer of sul-

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fathiazole sensitivity to normal human skin was reported by Shaffer, Lentz and McGuire<sup>26</sup> in cases of contact dermatitis due to topical use of the drug but similar tests with serums of other patients sensitive to sulfathiazole<sup>13</sup> and other sulfonamides<sup>18,27</sup> failed.

Recently, the authors have had the opportunity to study the serum of a patient who had an unusually severe reaction to sulfadiazine, and this serum showed the presence of a demonstrable skin-sensitizing antibody to that drug.

The patient, a twenty-four year old woman, was admitted to the Roosevelt Hospital, January 5, 1946, because of general erythema, vomiting, bloody diarrhea and collapse. There was no past history of allergic disease or drug reactions, but her mother had had hay fever. Six months before admission, the patient had taken sulfadiazine for several days for an upper respiratory infection, with no untoward reaction.

On the day before admission, she noticed a mild adenitis of the cervical lymph nodes, and was advised by a physician to take sulfadiazine. She took the first dose of 1.0 Gm. before dinner, and forty minutes later became acutely ill with a feeling of fullness in her head, severe itching and redness of the skin, followed by severe vomiting and diarrhea, with blood in the vomitus and stools. Within six hours, she was in a state of collapse with a rapid, thready pulse. During this same time, a single large bleb, approximately 5 cm. in diameter, appeared on her left buttock. Her leukocyte count was 20,000. The acute symptoms abated the next day and she made an uneventful recovery.

Intracutaneous tests with various foods were normal. A patch test with sulfadiazine powder showed a negative reaction, but when a patch test with 10 per cent sodium sulfadiazine was applied to the unbroken skin, the area began to itch within four minutes. When this patch was removed ninety minutes later, there was a definite wheal with erythema at the site. Because of the acuity of the patient's symptoms and the fact that a wheal reaction was obtained by application of the soluble salt of sulfadiazine to the unbroken skin, no scratch or intracutane-

ous test was attempted but blood for passive transfer was taken on the fifteenth day.

Passive transfer, carried out with the usual technic, showed a marked reaction to 1 per cent sodium sulfadiazine, with a wheal 1.5 cm. in diameter, while the control test on non-sensitized skin gave no reaction. Other sites tested with timothy and ragweed pollens, dog epithelium, feathers and house dust showed no reaction. The positive reaction to 1 per cent sodium sulfadiazine was demonstrated in skin sites sensitized with the same serum in six different normal test subjects, producing wheals

TABLE I  
PASSIVE TRANSFER REACTIONS OF DILUTIONS OF WA. SERUM  
WITH SULFONAMIDE DRUGS

Sites Made with Wa. Serum	Reaction On Test After 48 Hours With			
	Sodium Sulfadia- zine 1%	Sodium Sulfapyri- dine 1%	Sodium Sulfathia- zole 1%	Sulfa- nilamide Saturated Solution
Concen- trated	++++	++++	++++	0
1-10	++++	+++	+++	0
1-100	+++	++	++	0
1-1000	++	+	++	0
1-10,000	±	0	0	0
Control	0	0	0	0

1.4 to 2.0 cm. in diameter in all cases. Testing with 0.1 per cent sodium sulfadiazine gave a smaller but definite reaction. When the serum was heated four hours at 56°C., it no longer gave a definite transfer reaction to 1 per cent sodium sulfadiazine.

In another experiment, quadruplicate sites were sensitized with 0.1 ml. of serum and with dilutions of the serum 1-10, 1-100, 1-1000 and 1-10,000 in saline. One series of sites was tested with 1 per cent sodium sulfadiazine, another with 1 per cent sodium sulfapyridine, the third with 1 per cent sodium sulfathiazole, and the fourth with a saturated solution of sulfanilamide, which contains slightly less than 1 per cent. As shown in Table I, the first three drugs gave definite reactions in sites made with the 1-1000 dilution; sodium sulfadiazine gave a questionable reaction with the 1-10,000 dilution



FIG. 1. Reactions obtained on passive transfer. On left, sites made with Wa. serum, concentrated, 1-10, 1-100, 1-1000 and 1-10,000 respectively, tested with 1 per cent sodium sulfadiazine. On right, sites made with Wa. serum (undiluted) tested with 1 per cent sodium sulfadiazine, 1 per cent sodium sulfapyridine, 1 per cent sodium sulfathiazole, and saturated solution of sulfanilamide. Control tests on non-sensitized skin at extreme right.

of the serum, while sulfanilamide gave no reaction. The failure of sulfanilamide to react was not due to its slightly lower concentration, since in another experiment a similar serum site had been shown to react definitely with 0.1 per cent sodium sulfadiazine.

Figure 1 illustrates the results of a similar but less complete test in which serial dilu-

tions of serum were tested with 1 per cent sodium sulfadiazine, but only sites of the undiluted serum were tested with the other drugs.

For a neutralization experiment, the sensitive serum was mixed with equal volumes of solutions of sodium sulfadiazine of various strengths (0.1 per cent, 1 per cent and 10 per

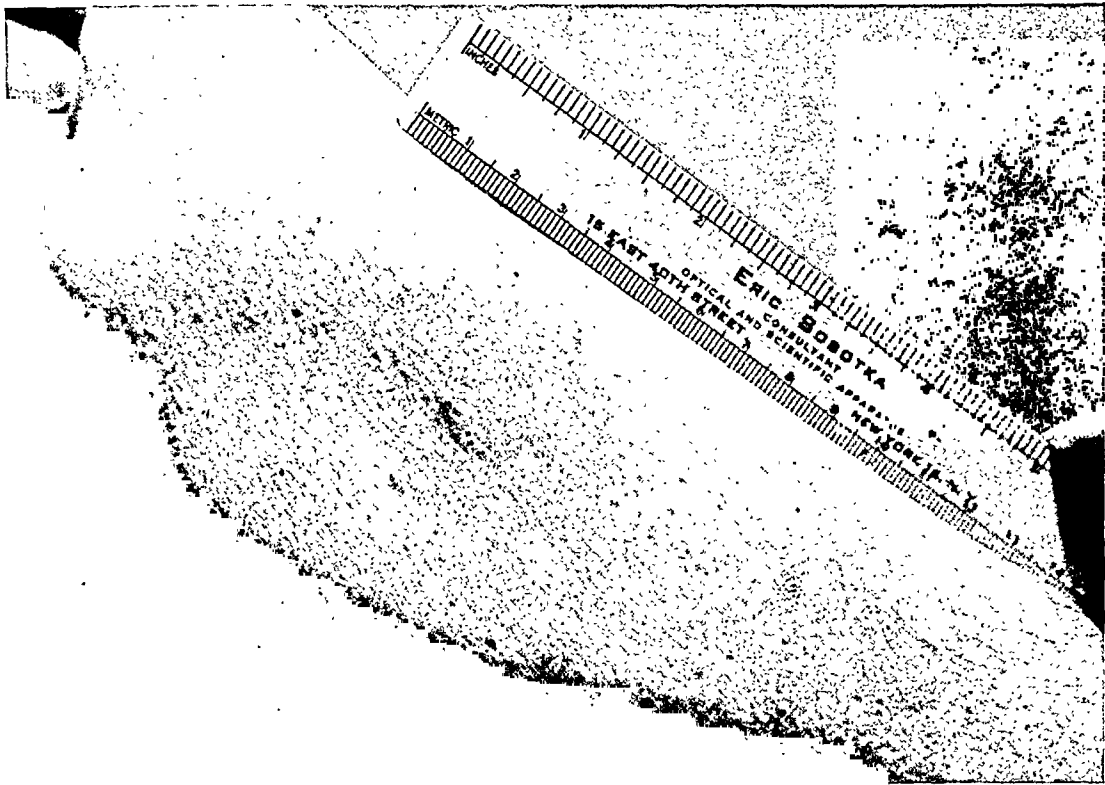


FIG. 2. Reaction produced in sensitized site by ingestion of 1.0 Gm. of sulfadiazine.

cent respectively); with serum from a patient receiving sulfadiazine; and as a control, with saline. When sites in normal skin were sensitized with these mixtures and tested forty-eight hours later with 1 per cent sodium sulfadiazine, all reacted approximately equally, showing no evidence of neutralization of the skin-sensitizing antibody. The same sites were tested a second time, twenty-four hours later, with 1 per cent sodium sulfadiazine, and again showed strong reactions, indicating that the antibody had not been neutralized or exhausted by the first testing.

In other experiments, a sensitized site was not tested intracutaneously, but the test subject ingested 1.0 Gm. of sulfadiazine. In four such tests a strong reaction with a wheal 2 to 3 cm. in diameter, and a surrounding red erythema 6 to 7 cm. in diameter appeared in forty to ninety minutes. (Fig. 2.) Ingestion of 2.0 Gm. of sulfanilamide or 1.0 Gm. of sulfapyridine gave no reaction. Ingestion of 1.0 Gm. of sulfa-

thiazole gave rise to an area of redness and itching, 3 by 5 cm., at the sensitized site, appearing two and a half hours later and lasting two hours without wheal formation. The day after the ingestion of these other drugs, the site was tested by ingestion of sulfadiazine and reacted strongly. When sulfadiazine was ingested a second time, after two days, there was no reaction, indicating that the antibody was exhausted or neutralized by this method of testing.

Precipitin tests with the sensitive serum and various dilutions of sodium sulfadiazine were negative. An attempt to sensitize the skin of a guinea pig by the intracutaneous injection of 0.1 ml. of the serum gave negative results. Two ml. of serum were also injected intra-abdominally into a virgin female guinea pig and a Dale test performed two days later. There was no reaction with sodium sulfadiazine, although the control test with histamine gave an active contraction.

On the basis of these observations, sulfa-

diazine may be added to the simple chemical compounds which have been shown to stimulate the formation of demonstrable antibodies in the human body and to react with these antibodies in the passively sensitized skin site. Since the plasma proteins have been shown to bind sulfadiazine,<sup>28</sup> one may assume that such a reaction takes place to form a protein antigen. There is nothing in the observed facts to prove or disprove this hypothesis, but if the combination is assumed to take place in the sensitized site, it must occur almost instantaneously, since the urticarial reaction is just as rapid as with typical protein antigens.

The skin-sensitizing antibody in this serum resembled that of a highly sensitive hay fever patient in its activity (as measured by the dilution test), in its thermolability, in its failure to sensitize passively a guinea pig and in its failure to form a precipitate with the antigen. It differed in that the antibody was not easily neutralized by the antigen *in vivo* or *in vitro*. However, the difference may have been in the allergen rather than the antibody, the rapid diffusibility of sulfadiazine removing it from the site before the antibody was completely neutralized.

Similar studies of the serums of two other patients known to be sensitive to sulfadiazine, one of whom had a severe general reaction 20 minutes after taking 1 Gm. of the drug, showed no demonstrable skin-sensitizing antibody. These observations and the reports of other cases in the literature, suggest that the passive transfer of sensitivity to sulfadiazine is rare. It is doubtful if this method will often prove useful in diagnosis. However, the fact that it may occur is of interest and might occasionally be of practical use.

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## Fungus Diseases Encountered in General Hospital Practice\*

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**S**UPERFICIAL fungus infections of skin, hair and nails are often chronic and resistant to treatment but rarely affect the general health of the patient. The deep mycoses are frequently fatal; they may be acute, subacute or chronic and present major problems in diagnosis and treatment.

### ACTINOMYCOSIS

The clinical syndrome of actinomycosis may be caused by either the anaerobic *Actinomyces bovis* or the several species of aerobic *Actinomyces* now called *Nocardia*.<sup>1</sup> *A. bovis* may be found in the gums and tonsils<sup>2,3,4,5</sup> of apparently healthy normal individuals, and various types of pathogenic *Nocardia* have been isolated from the soil.<sup>6</sup>

Approximately 90 per cent of actinomycetic infections are of the anaerobic type.<sup>6</sup> The disease occurs in all parts of the world and in all races. It is most prevalent between the ages of fifteen and thirty-five and affects men twice as frequently as women.

There are four clinical forms of the disease: (1) cervicofacial, (2) pulmonary, (3) abdominal and (4) generalized. The diagnosis should be suspected from the clinical picture, but must be confirmed by the demonstration of the characteristic organisms in pus, sputum, biopsy specimens (Fig. 1) or by the isolation of the organism on appropriate media. *A. bovis* should be grown in veal infusion medium under anaerobic con-

ditions. The aerobic *Nocardia* grow on blood agar or Sabouraud's medium.<sup>7</sup>

The prognosis is best in the cervicofacial form of the disease and becomes progressively worse in the pulmonary, abdominal and generalized infections.<sup>8-13</sup>

Both the aerobic and anaerobic types of actinomycosis respond slowly to treatment with either sulfonamides or penicillin.<sup>14,15,16</sup> A few patients have been cured by chemotherapy, but in many instances the symptoms persist or the apparently cured patient relapses after some months. Extensive and repeated surgery is required frequently, not only for drainage of abscesses but for the destruction and elimination of as much as possible of the infected tissue. Iodide therapy is of little value alone but should be used as a supplement to chemotherapy to promote resolution and absorption of granulomatous tissue. X-ray therapy has been used to stimulate the healing of indolent lesions.

### PARA-ACTINOMYCOSIS

A number of organisms belonging to the family of Actinomycetaceae have some superficial resemblance to *Actinomyces* and produce subacute and chronic infections which must be differentiated from cases of true actinomycosis. These infections are known in the literature as (1) mycotic rat-bite fever,<sup>17</sup> (2) Haverhill fever,<sup>18</sup> (3) erysipeloid,<sup>19,20,21</sup> (4) *Bacteroides* infection,<sup>23,24,25</sup> (5) actinobacillosis<sup>26,27</sup> and (6)

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FIG. 1. *Actinomyces bovis*. A, granule in pus from draining sinus.  $\times 162$ ; B, crushed granule stained by Gram's method to show gram-positive branching filaments.  $\times 1080$ .



FIG. 2. *Blastomyces dermatitidis*. A, filamentous form of room temperature culture on Sabouraud's glucose agar.  $\times 658$ ; B, budding yeast-like form in pus from lesion.  $\times 762$ .

botryomycosis or staphylococcic actinophytosis.<sup>28</sup> This last mentioned infection is caused by a *Staphylococcus*, but one that produces, for some unknown reason, chronic granulomatous lesions with draining sinuses and "granule" formation which under the low power of the microscope resembles closely the typical "sulfur granule" of *A. bovis*.

#### NORTH AMERICAN BLASTOMYCOSIS

Blastomycosis is caused by *Blastomyces dermatitidis*. This is an exogenous infection but its source in nature has not been discovered.<sup>29</sup> A few instances of the disease have been reported from England, but all

the other authentic cases have occurred within the borders of the United States and Canada.<sup>30</sup> It occurs with greatest frequency in the Mississippi Valley and in the Southeastern states.<sup>31</sup> It may begin at any age between six months and eighty years, but is most often seen between the ages of twenty and forty. All races are susceptible, but males are infected nine times as frequently as females.

Two characteristic clinical forms of blastomycosis are known: (1) the cutaneous and (2) the systemic. The cutaneous form is



chronic and may persist for eight to ten years before spreading to the internal organs.<sup>32,33</sup> The systemic form of the disease is more acute, usually resulting in death in six months to three years.<sup>31,34</sup> Most of the systemic cases begin in the lungs, suggesting inhalation as the mode of infection.

The diagnosis is established by finding the characteristic double-contoured budding forms in pus, sputum and biopsy material or by culturing the organism on Sabouraud's medium. (Fig. 2.) Progressive cases usually have complement-fixing antibodies present in the serum.<sup>35</sup> The patients may or may not have positive skin tests of the delayed tuberculin type to autogenous or stock cultures of *B. dermatitidis*.

The prognosis is good in cutaneous blastomycosis, grave in the pulmonary form and usually hopeless in the generalized cases.

Potassium, sodium and ethyl iodide have all been used in the treatment of blastomycosis, but the results of iodide therapy are modified by the immunologic status of the patient. Patients with definitely positive skin tests should be desensitized with vaccine or antigen before iodides are administered, since a failure to desensitize may result in a lack of improvement or even a prompt exacerbation of the infection. Patients with slightly positive skin tests may be successfully treated with large doses of iodides.

Occasionally, instances are encountered in which the patient has no evidence of immunity as indicated by negative skin tests and negative complement-fixing antibodies. These negative findings may result from (1) an excess of antigen in the tissues, as in the case reported by Martin<sup>35</sup> in which the intradermal injection of immune rabbit serum resulted in an immediate wheal reaction, or (2) a total lack of immunity. In Martin's case immune rabbit serum reversed the immunologic processes. Where there is no evidence of immunity, stock or

autogenous vaccines should be administered until the patient has complement-fixing antibodies in the serum before the administration of iodides.

X-ray therapy is effective in cutaneous blastomycosis after desensitization of the hypersensitive and while iodides are being administered.

#### COCCIDIOIDOMYCOSIS

Coccidioidomycosis is an exogenous infection caused by *Coccidioides immitis*. Emmons<sup>36,37</sup> discovered that the infection is endemic in rodents in the arid areas of the Southwest. After the death of the rodent the fungus develops resistant chlamydospores which persist in the soil for an indefinite period of time where they may be introduced into the skin following an injury or breathed into the lungs of man and animals with dust. Davis, Smith and Smith<sup>38</sup> have isolated the organism from the soil.

With the exception of three cases from Italy and four cases from South America, all the other authentic instances of the disease have originated in the Southwestern states.<sup>30</sup>

This disease has been found as early as three months of age and has developed as late as seventy years, but is most prevalent between twenty-five and thirty-five. The progressive granulomatous form of the disease develops most frequently in the deeply pigmented races, such as Negroes, Filipinos, Indians and Mexicans. Laboratory workers may be infected by the accidental inhalation of powdery material from old, dry cultures. Males are more often infected with the progressive disease than females.

The physician should recognize (1) primary coccidioidomycosis which is usually an acute but benign, self-limiting respiratory infection and differentiate it from (2) progressive coccidioidomycosis which is a chronic, malignant, disseminated disease

that involves cutaneous, subcutaneous, visceral and osseous tissues.

The high incidence of positive skin tests to coccidioidin (70 to 80 per cent) in certain areas in the Southwest suggests that most cases of primary coccidioidomycosis either are asymptomatic or cannot be differentiated from mild non-specific respiratory infections.<sup>39-42</sup> Goldstein and McDonald's observations<sup>43</sup> on seventy-five soldiers who developed the primary form of the disease while on maneuvers in the desert showed that the incubation period ranged from one to three weeks. The symptoms were respiratory and the physical findings minimal. After eight to fourteen days skin lesions, usually of the erythema nodosum type (19 per cent), and arthralgia (28 per cent) developed.<sup>43,44,45</sup> This form of the disease has been known for years as "valley fever," "desert rheumatism" or "desert fever." X-ray studies showed hilar enlargement, fan-like lesions in the parenchyma of the lungs and occasional pleurisy. Thin-walled pulmonary cavities developed in 4 per cent.<sup>46-49</sup>

The intradermal injection of 0.1 cc. of a 1:1000 dilution of a standardized coccidioidin usually gives a positive reaction after two weeks of illness, and this sensitivity persists for many years.<sup>50</sup> Precipitins and complement-fixing antibodies are absent in mild cases but appear in the more severe infections, only to disappear with recovery.

There is usually an initial leukocytosis, frequently followed by an eosinophilia and accompanied by an increase in the sedimentation rate.

Progressive coccidioidomycosis usually develops from the more severe cases of the primary disease although theoretically it is possible for the infection to originate from an inadequately healed lymph node in a manner analogous to reinfection pulmonary tuberculosis.<sup>51</sup>

The persistence of an elevated sedimen-

tation rate, the development of a high precipitin and complement-fixing titer and the appearance of new parenchymal shadows in the x-ray suggest the development of the progressive form of the disease. In a fully developed case, the symptoms, physical signs and x-ray shadows resemble those found in cases of reinfection tuberculosis with pulmonary and extra-pulmonary lesions.<sup>52-59</sup>

In primary coccidioidomycosis, *Coccidioides immitis* usually can be grown on Sabouraud's medium from the mucoid sputum although the characteristic spherules are rarely found. (Fig. 3.) The spherules are generally present in abundance in the sputum and abscesses of the progressive form of the disease.

The prognosis usually is excellent in primary coccidioidomycosis and very poor in the progressive form of the disease.

The treatment is symptomatic in the primary infection. The patient should be confined to bed until the temperature, white blood count and sedimentation rate are normal. Persistent thin-walled cavities frequently heal after a period of months but the resistant ones, particularly when complicated by repeated hemoptyses, may have to be eliminated by a lobectomy.<sup>60</sup>

Progressive coccidioidomycosis responds poorly to treatment. Iodides without desensitization are useless and are of questionable value even after desensitization.

#### HISTOPLASMOSIS

Histoplasmosis is caused by *Histoplasma capsulatum* which is usually found in the cytoplasm of endothelial and mononuclear cells.<sup>30</sup>

The source of the infection has not been found in nature. A few spontaneous infections have occurred in dogs,<sup>61,62,63</sup> but it is probable that these animals, like man, are the victims and not the reservoir of infection.

Occasional cases of histoplasmosis have

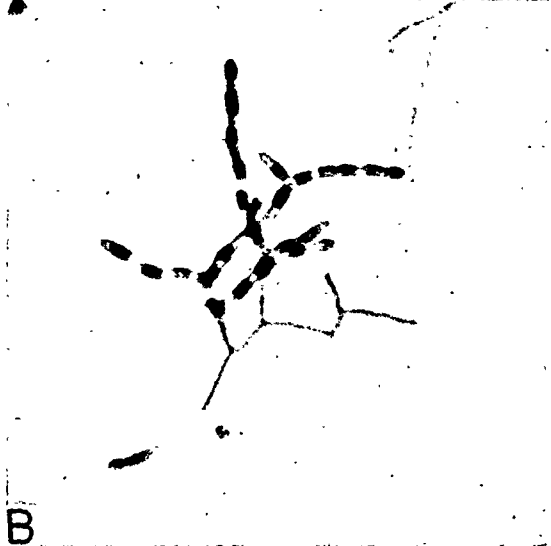
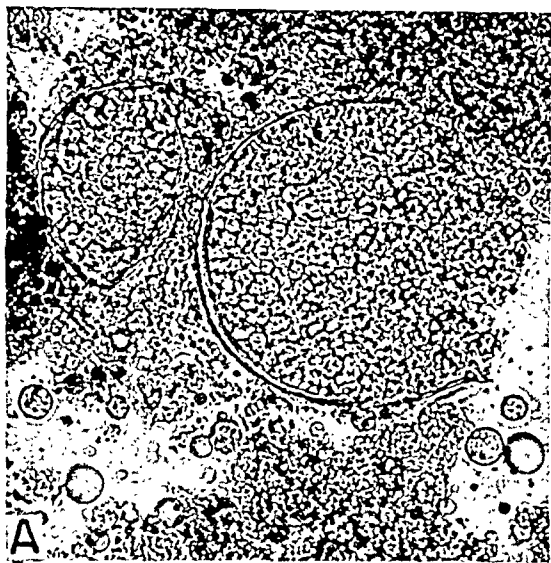


FIG. 3. *Coccidioides immitis*. A, large endospore-filled spherule in pus.  $\times 315$ ; B, filamentous form taken from Sabouraud's glucose agar at room temperature.  $\times 658$ .

been recognized in widely scattered areas throughout the world although most instances of the disease have occurred in the United States and one-third of these in the states of Michigan, Missouri, Tennessee and Illinois.<sup>64</sup>

Young children are very susceptible to the disease. The youngest patient was one month, and ten other cases have developed in the first twelve months. Both sexes are affected equally up to the age of ten years. After the age of ten, males contract the disease seven times as frequently as females. All races seem to be equally susceptible.

Darling's original cases<sup>65</sup> were characterized by fever, emaciation, anemia, leukopenia, splenomegaly and hepatomegaly. Perhaps this is the syndrome which develops following an invasion through the intestinal tract since De Monbreun<sup>62</sup> has infected young dogs by feeding them cultures of *H. capsulatum*.

A recent review<sup>66</sup> shows that one-third of the reported cases began in the ear, nose, lips, mouth, pharynx and larynx. Enlarged lymph nodes were found in the neck, but hepatomegaly and splenomegaly were inconspicuous or a late development.

The lungs are nearly always involved in the terminal dissemination of the generalized cases, but a primary invasion of the lungs was thought to be a rare occurrence before the recent studies on the origin of non-tuberculous calcification revealed some surprising information. Smith, of California,<sup>67</sup> suggested that the central Mississippi Valley region, where there is a high incidence of pulmonary calcification in tuberculin-negative individuals, might be an endemic area of histoplasmosis. Christie and Peterson<sup>68</sup> and Palmer and his associates<sup>69,70</sup> have shown that there is a close correlation between the occurrence of pulmonary calcification in tuberculin-negative patients and the presence of a positive skin test to histoplasmin. A search is being made in the endemic area for a mild respiratory infection which might correspond to the benign primary coccidioidomycosis in the Southwest.

The intracellular tissue form of the parasite has a superficial resemblance to the Donovan bodies of leishmaniasis. They may be identified in smears of blood, bone marrow, lymph nodes, spleen or in biopsy specimens. The tissue form of the parasite will grow at 37°C. for a time on blood agar or other rich media but soon changes over, particularly at room temperature, to the saprophytic mold-like growth. (Fig. 4.)<sup>71-75</sup>

Histoplasmosis has been uniformly fatal except in a few cases in which the infection has been limited to a small lesion in the mouth.<sup>64</sup>

Treatment is unsatisfactory. Fuadin and neostam have been suggested.<sup>76</sup> Local applications of radium have been used successfully for ulcerations on the tongue.<sup>64</sup>

#### CRYPTOCOCCOSIS

Cryptococcosis, caused by *Cryptococcus neoformans*, is usually referred to as "blastomycosis" in the European literature and "torulosis" in the older American references.<sup>77,78,79</sup>

Spontaneous infections have been observed in animals, but direct spread from animal to man or from man to man has not been recorded. Benham has isolated from normal human skin<sup>80</sup> cryptococci culturally identical with *C. neoformans* but with slight pathogenicity for animals.

*Cryptococcus* infections have been encountered in all parts of the world. In this country most of the cases have been reported from the eastern seaboard region and in a zone extending across the southern states from Florida to California.<sup>30</sup>

The disease may occur at any age from ten to seventy years, but is most prevalent between forty and sixty. Males are infected almost twice as often as females, and all races seem to be equally susceptible.

*C. neoformans* may produce (1) a primary infection of the lungs which simulates tuberculosis or neoplasm,<sup>81</sup> (2) superficial ulceration of the skin with multiple sinuses, as in the original case reported by Busse and Buschke,<sup>82</sup> (3) subcutaneous nodules or abscesses which resemble myxomatous tumors,<sup>83</sup> or (4) a primary meningitis which may be confused with tuberculous meningitis. The organism has a marked predilection for the brain and meninges, and many cases beginning in the skin or lungs terminate with a meningitis.<sup>78,84,85,86</sup>

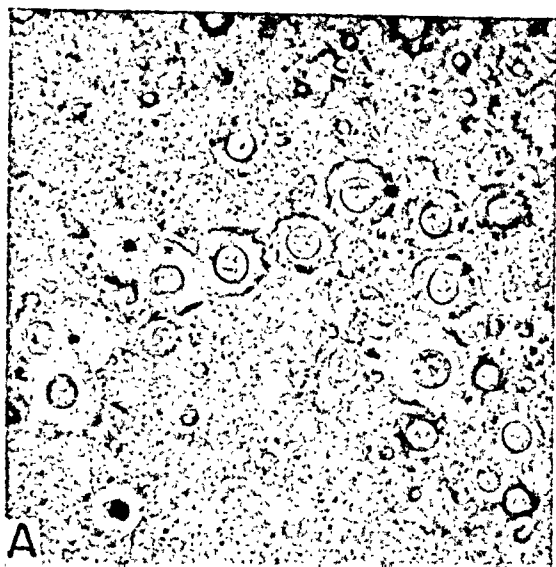


FIG. 4. *Histoplasma capsulatum*. A, yeast-like form cultured on blood agar at 37°C.  $\times 700$ ; B, filamentous form with large, tuberculate chlamydospores from Sabouraud's glucose agar.  $\times 658$ .

The organism multiplies by simple budding and is characterized by the presence of a large mucoid gelatinous capsule which is easily identified in tissue, spinal fluid or in cultures. (Fig. 5.)

The prognosis is poor in the skin and subcutaneous forms, worse in the pulmonary and practically hopeless in the cerebral and meningeal infections.

Nearly all of the authentic cases of cryptococcosis have terminated in death. Reeves,



B

FIG. 5. *Cryptococcus neoformans*. A, in pus.  $\times 684$ ; B, in pus. India ink preparation.  $\times 684$ .

Butt and Hammack<sup>87</sup> have cured one patient with sulfapyridine, Marshall and Teed<sup>88</sup> another with sulfadiazine. We have seen one case of pulmonary cryptococcosis improve with sulfadiazine and another apparently cured after prolonged treatment with this drug. Recently Jones and Klinck<sup>89</sup> reported a case which failed to improve with sulfadiazine or penicillin. Mice infected with the culture isolated from the patient were not protected by either sulfadiazine or penicillin.

#### MONILIASIS

Moniliasis, usually caused by *Candida albicans*, is almost certainly an endogenous infection since pathogenic strains have been isolated from the mouth, vagina and intestinal tract of normal individuals.<sup>30</sup>

Moniliasis has been found in all parts of the world. It occurs at all ages, in all races and in both sexes. Occasionally, the infec-

tion is contagious, and true epidemics of cutaneous moniliasis have occurred in fruit packers. Balanoposthitis has been observed in the husbands of women with *C. albicans* vaginitis, and cutaneous moniliasis has occurred about the nipples of mothers nursing infants with oral thrush. Moniliasis of the oral mucous membranes occurs most often in infants and elderly people with wasting diseases. Maceration of the hands in water predisposes to dermal and onychial lesions, poorly fitting dentures to oral lesions and diabetes and pregnancy to vaginitis.<sup>90-96</sup>

Bronchitis,<sup>97</sup> pneumonitis,<sup>98-100</sup> meningitis,<sup>101</sup> endocarditis<sup>102,103</sup> and osteomyelitis<sup>104</sup> have all been reported. In many instances the *Monilia* infections are secondary to some more serious condition, but in other instances they are without doubt the primary cause of the disease. In many individual cases the differentiation between primary and secondary invader is almost impossible even with the aid of the laboratory.<sup>97</sup>

In most instances both the budding yeast-like and hyphal forms of the organism can be found without difficulty in fresh wet preparations. (Fig. 6.) Even when the direct examination is negative, positive cultures are easily obtained on Sabouraud's medium or simple agar containing 1 per cent dextrose and adjusted to a pH of 5-6.<sup>105,106</sup>

The localized types of oral, vulvovaginal and cutaneous moniliasis frequently respond readily to treatment, only to relapse when the predisposing factors are duplicated. The chronic types of glossitis and vulvovaginitis may persist for years. Cutaneous moniliasis in hypersensitive patients responds poorly to therapy. Some forms of bronchial and pulmonary infection respond readily to iodide therapy, while others are extremely resistant. The prognosis is hopeless in patients with endocarditis or meningitis.

The dermal and onychial infections should be referred to a dermatologist.

Acute oral lesions respond to simple alkaline mouth washes or a dilute solution of gentian violet. Chronic oral lesions in hypersensitive patients may clear up after careful desensitization. Alter and his associates in the Duke clinic<sup>107</sup> are now obtaining excellent results in chronic cases of vaginitis, which resisted all previous treatment, with a jelly-like preparation of sodium propionate. It is still too soon to conclude that the cures will be permanent.

Bronchial and pulmonary moniliasis usually respond readily to iodide therapy if the patients have not developed a hypersensitivity. When the hypersensitive patient is desensitized and treated cautiously with iodides, the improvement is slow but progressive. Intravenous gentian violet<sup>30,98</sup> has been used successfully in some of the acute pulmonary cases. A rare immunologic type of pulmonary moniliasis recently reported by Hiatt and Martin<sup>108</sup> was cured with immune rabbit serum.

#### SPOROTRICHOSIS

Sporotrichosis is caused by *Sporotrichum Schenckii* which is primarily a saprophyte or parasite of plants.<sup>109</sup> It has been found in nature on thorns, ferns and the bark of trees. Du Toit<sup>110</sup> isolated the organism from timber and mud in a mine in South Africa. Spontaneous sporotrichosis has been observed in horses, dogs, cats, rabbits and rats. Foerster<sup>111,112</sup> reported two instances of the disease in man acquired by handling contaminated dressings, and Meyer<sup>113</sup> infected himself with a culture isolated from a horse.

Sporotrichosis has been found in all parts of the world but appears to be most prevalent in the north central Mississippi Valley and in France.<sup>30</sup>

The disease has been observed at all ages from sixteen months to seventy-one years. One case out of five occurs in children; males are most frequently infected, especially farmers, laborers and horticulturists.



FIG. 6. *Candida* (*Monilia*) *albicans*. From Sabouraud's glucose agar at room temperature.  $\times 658$ .

A surprising number of cases have followed the prick of a barberry thorn.<sup>112</sup>

According to De Beurmann and Gougerot,<sup>114</sup> the disease may be divided into six clinical types: (1) lymphatic, (2) disseminated, (3) epidermal, (4) mucosal, (5) skeletal and (6) visceral. To these one should add (7) the pseudoneoplastic form recently described by Smith.<sup>115</sup>

The tissue form of the disease is a small, gram-positive, cigar-shaped body which is found in the cytoplasm of monocytes, giant cells and leukocytes. The organisms are rarely seen in biopsies of human material, but appear in abundance when the infected tissues are inoculated into rats. During the past year Campbell<sup>116</sup> succeeded in growing the tissue form of the organism by culturing it on the cystine agar designed by Francis for the isolation of *Pasteurella tularensis*.

The mold-like or saprophytic form of organism grows readily on Sabouraud's medium (Fig. 7) after ten to twenty days' incubation.

The prognosis is excellent in the very common lymphatic forms and the less com-

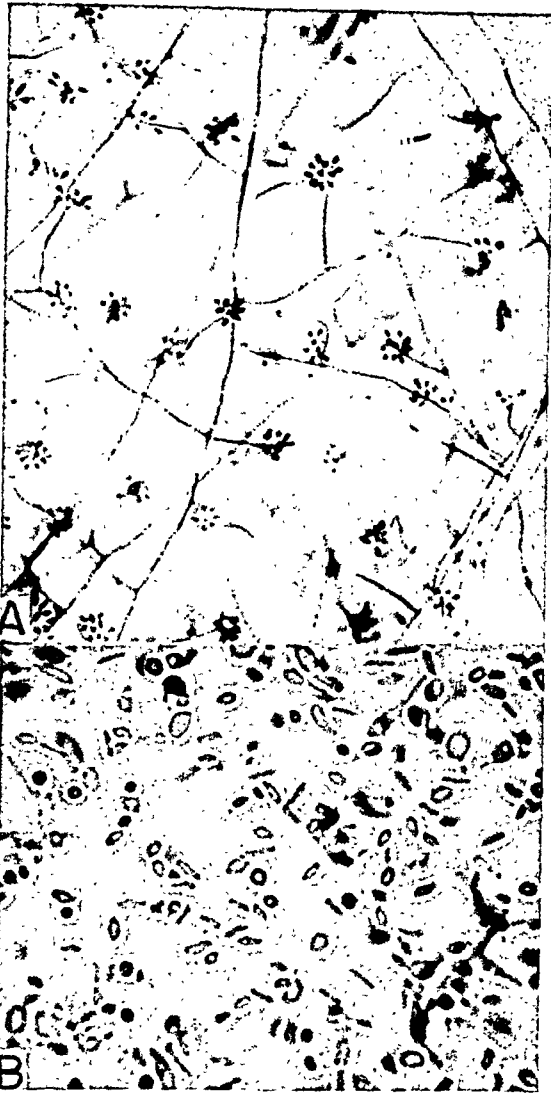


FIG. 7. *Sporotrichum schenckii*. A, filamentous form on Sabouraud's glucose agar at room temperature.  $\times 658$ ; B, tissue form taken from cystine agar culture at  $37^{\circ}\text{C}$ .  $\times 762$ .

mon pseudoneoplastic type but is poor in the rarer disseminated and visceral infections.<sup>117</sup>

Potassium iodide is practically a specific in the treatment of sporotrichosis, but large doses should be employed and continued for four to six weeks after apparent recovery. An occasional case may require supplementary vaccine therapy.

#### MADUROMYCOSIS

Maduromycosis is a chronic infection usually of the feet but occasionally of the hands or other parts of the body. It is char-



FIG. 8. Maduromycosis. Large granule found in section (case due to *Monosporium apiospermum*).  $\times 112$ .

acterized by chronicity, tumefaction and multiple sinus formation. Identical clinical pictures may be caused by any one of thirteen species of *Actinomyces* or any one of twenty-two species of molds belonging to two classes and nine genera.<sup>30,118</sup>

The source of the infection is evidently exogenous since more than one-half of the patients give a history of an injury such as a minor scratch, bruise or splinter wound.<sup>119</sup>

The disease occurs most frequently in the tropics and in the southern part of this country.<sup>120,121</sup> The infection may start at any age from eight to eighty, but is most prevalent between the twenty-first and fortieth year. Males are infected nine times as often as females, and most cases have occurred in agricultural workers.

The diagnosis is established by finding the characteristic "grains" in the serosanguineous or "oily" fluid which exudes from the sinuses. The granules may be yellow, white, orchid, red or black, but are not characteristic of any particular type of fungus. (Fig. 8.) About 50 per cent of the cases are caused by the various species of



FIG. 9. Chromoblastomycosis. Small, thick-walled, brown bodies found in pus, crusts or section. (Case due to *Hormodendrum Pedrosoi*.)  $\times 816$ . (W. B. Saunders Co., Manual of Clinical Mycology, 1944.)

*Actinomyces* and the other half by the mold-like fungi.

The prognosis is poor, the patient usually dying of secondary infection.

Maduromycosis caused by *Actinomyces* may respond to sulfonamide<sup>122</sup> and penicillin therapy supplemented by surgical drainage. Those that resist this treatment and all of the cases caused by molds should be treated by amputation of the limb before the patient is debilitated by secondary infections.

#### CHROMOBLASTOMYCOSIS

Chromoblastomycosis is characterized by the formation of warty cutaneous nodules which develop slowly into papillomatous vegetations. *Hormodendrum Pedrosoi*, *Hormodendrum compactum* and *Phialophora verrucosa* all produce identical clinical lesions.<sup>30,123</sup>

These organisms exist in nature as saprophytes or parasites of wood. Weidman and Rosenthal<sup>124</sup> found that most cases developed following an injury by some form of wood, either living or dead. Conant and Martin<sup>125</sup> proved that certain strains of



FIG. 10. *Rhinosporidium Seeberi*. Sporangium containing spores in section from nasal polyp.  $\times 175$ . (W. B. Saunders Co. Manual of Clinical Mycology, 1944.)

*Phialophora*, isolated by Kress and his associates from wood pulp, were morphologically and serologically identical with strains of *P. verrucosa* isolated from patients.

The disease occurs sporadically throughout the world and is most prevalent between the ages of thirty and fifty. All races are equally susceptible and males are infected thirty-four times as frequently as females.

The lesions begin as small itchy papules and evolve slowly over months or years without affecting the general health of the patient. The lesions are most often confused with those of blastomycosis or neoplasms.<sup>126</sup>

The diagnosis is established by the demonstration of dark brown septate bodies in pus or biopsy specimens. (Fig. 9.) The mold-like forms of the organism grow readily on Sabouraud's medium.

The disease is almost never fatal, but it is not curable except in its earliest forms.

Complete surgical excision is the treatment of choice for the early lesions.<sup>127</sup> Iodides by mouth and local iontophoresis<sup>128</sup> improves but does not cure the advanced cases.



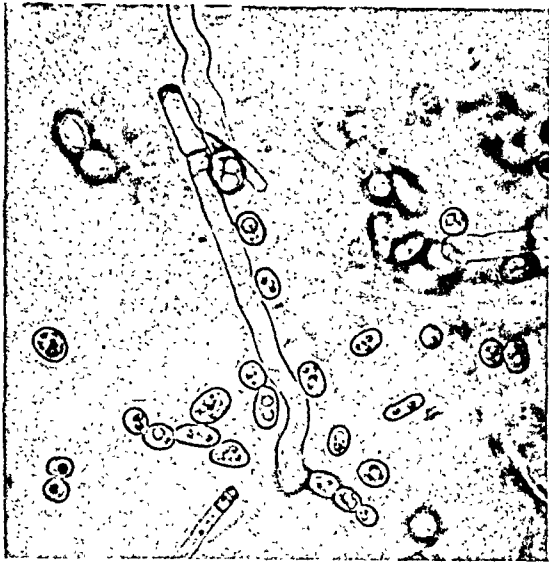


FIG. 11. *Geotrichum* sp. From Sabouraud's glucose agar at room temperature.  $\times 658$ .

#### RHINOSPORIDIOSIS

Rhinosporidiosis is caused by *Rhinosporidium seeberi* which produces friable, sessile or pedunculated polyps of the mucous membranes of the nose, eyes and larynx. Occasionally, lesions develop in the ears, vagina, penis and skin.

Epidemiological studies suggest that the infection is acquired by swimming or diving in stagnant water.<sup>129</sup>

This disease is endemic in India and Ceylon<sup>129,130</sup> but occurs sporadically in various parts of the world, including the United States. The infection is most common in children and young adults. The first thirteen cases reported in this country were all in males.<sup>30</sup>

Both the polypoid form in the nose<sup>131</sup> and the sessile form in the eye<sup>132,133</sup> have occurred in this country.

The diagnosis is established by the demonstration in smears of the round to oval spores, 7 to 9  $\mu$  in diameter, or by the discovery in biopsy of the characteristic spore-filled sporangia. (Fig. 10.)

Rhinosporidiosis is rarely fatal, but the patients may succumb to secondary infections.

Complete surgical removal effects a cure.

The advanced cases are improved by pentavalent antimony compounds.<sup>129</sup>

#### GEOTRICHOSIS

Geotrichosis, caused by one or more species of *Geotrichum*, occasionally produces lesions of the mucous membranes which resemble thrush and infections of the bronchi and lungs which simulate other types of mycotic disease.<sup>30,134</sup>

The presence of thin-walled cavities in the parenchyma of the lungs may suggest a clinical diagnosis of primary coccidioidomycosis.<sup>135</sup> In the laboratory, the double-contoured budding cells of the tissue form of the organism may be mistaken for *Blastomyces*, but the accompanying rectangular spores are characteristic and diagnostic. (Fig. 11.)

The prognosis is usually good with iodide therapy.

#### ASPERGILLOSIS, PENICILLIOSIS AND MUCORMYCOSIS

These molds frequently produce infections in the external ear. Occasionally, granulomatous lesions appear in the skin, nasal sinuses, orbit, bronchi, lungs and other internal organs.<sup>136-144</sup> Squab feeders, fur cleaners and agricultural workers who are exposed to clouds of spores may become infected.<sup>30</sup>

The prognosis is good except for the pulmonary and generalized infections which are frequently fatal.

Iodides are used for treatment but hypersensitive patients should be desensitized.

#### CONIOSPORIOSIS

A peculiar type of pneumonitis, presumably allergic, occurs in laborers in the northern forests who are repeatedly exposed to the inhalation of spores of *Coniosporium corticale* growing on the inner bark of maple logs.<sup>145</sup>

The patients recover when removed from contact with the spores.

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# Seminars on Rheumatic Fever

## Rheumatic Fever in the Perspective of Public Health\*

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IN presenting this subject, I should like to emphasize certain points as a preliminary to what is to follow. First, I am not an expert in rheumatic fever. Second, I shall not be concerned with the question of etiology or the relative importance of heredity and environment; nor shall I go into the question of whether in rheumatic fever and rheumatic heart disease, there is one continuing disease or a series of fortuitous episodes. However, in using the term rheumatic fever I intend to include rheumatic heart disease. Finally, I shall attempt to discuss rheumatic fever in the perspective of public health as a whole, approaching the matter broadly and at first without specific reference to any particular disease. I give you this latter warning because in the text of this paper rheumatic fever itself will not be discussed until a background is sketched in.

Now, in the long and sometimes stumbling history of the acquisition of scientific knowledge, it is noticeable that most progress has been made by those with a singleness of interest and purpose. But it is equally noticeable that knowledge becomes widely useful and usable only when it reaches the stage of simple expression and uncomplicated application. It would seem entirely proper, therefore, that groups of scientists here and there focus their respective interests and research in comparatively

narrow fields provided, at the same time, mechanisms are ensured for translating the new knowledge that they gain into applied measures for the benefit of mankind. To do both these things is, ordinarily, quite difficult but in the past few decades, the rapidity with which new fundamental knowledge has been acquired and, correspondingly, the opportunity for its utilization and even the demand for its application have been such as to create a problem of its own. Thus workers in more general fields, and society as a whole, have encountered difficulty in deciding what future emphasis should be given to research in this direction or that, and to what extent efforts in control of one disease or another might and should be undertaken.

To make decisions of this sort is not easy nor can such a choice be made without the hazard of error, because of the multiplicity of causes of ill health and death. Thus, in the manual of the International List of Causes of Death, 200 separate causes are recorded; and in the Standard Nomenclature of Diseases, published by the American Medical Association, and the Manual for Coding Causes of Illness, issued by the United States Public Health Service, there are about 1,000 causes of morbidity listed. It is obvious, of course, that some causes of illness and death are a greater drain upon the public health than others—cancer in

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comparison with German measles, for instance. It is equally obvious, too, that the amount of time or money spent by official and voluntary health agencies in efforts to gain new knowledge or to control various public health problems is not in proportion to the public health seriousness of the various diseases. But it would be unsafe to proceed on the basis of "obviousness" to decide, from a public health standpoint, the relative seriousness of any one of the 200 causes of death or the 1,000 conditions that may cause illness. *Some sharper and more objective guide than this is necessary.*

Unfortunately, the very nature of the matter under discussion makes it impossible to ensure exact analysis of each of the factors that contributes to the seriousness of any given disease or to weigh these factors. In certain instances, our knowledge and our methods are not sufficiently refined even to discover all the factors that contribute to mortality and morbidity; and even when those factors are discovered, certain human and sociological values and potentials enter so strongly into the situation as to make quantitative expression impossible except as approximations. Similarly, it is not practicable to evaluate all those interacting forces that influence society's decision as to how much time and money might profitably be allocated to any given disease. Nevertheless, it is possible to approach objectively this matter of determining the relative seriousness of disease and, even though complete assay is not attainable, there are at hand certain criteria for judging the relative seriousness of diseases. There are certain others that will bring to light those influences that shape public health practice.

The factors that express the seriousness of a public health problem may be expressed broadly as mortality, morbidity and the age group in which the forces of mortality and morbidity manifest themselves. Each of these elements justifies further discussion.

In attempting to determine the social and even biological burden of mortality from any given cause, it is necessary, of course, that the data from which conclusions are drawn be accurate and complete. One must take into consideration also the accuracy of original observations, the nomenclature and definitions used in the past as compared with the present, the sharpness of diagnosis possible twenty-five years ago and today, and diagnosis in medical center areas as against locations where diagnostic acumen and facilities are not the best. Not only must these factors be considered in relation to the cause of death in question, but also in relation to other causes of death. This necessity is obvious because one must view mortality from a single cause not only in absolute numbers but also proportionately, that is, how much of the total mortality does this single cause bring about. For it would be possible for the number of deaths from a given cause to remain the same, or even for a rate to remain the same, and yet the disease might be of relatively more or less importance than formerly because of increases or decreases in mortality from other causes. One might remain in ignorance of this shift if proportionate mortality is not studied.

If one uses small numbers and data reflecting short experience in considering mortality data, great care must be exercised in interpretation of them lest extraneous influences and chance enter into the picture. Having assured oneself of these safeguards, it would seem reasonable to conclude that, other things being equal, a disease that brought about 25,000 deaths a year and constituted 5 per cent of the total mortality would constitute a more serious public health problem than would one that caused but 2,500 deaths a year and constituted 0.5 per cent of all deaths.

The use of morbidity data as an index of the seriousness of disease must be safe-

guarded by those considerations just set forth in relation to mortality. Similarly, from a community standpoint, one would consider the seriousness of a disease in relation to morbidity somewhat in proportion to the number of cases that occur each year. But, as is the case in considering mortality, there are other factors that must be taken into consideration in relation to morbidity.

The first of these is *case fatality*. It needs no argument to bring out the fact that 1,000 cases of dengue are not nearly so serious as a much smaller number of cases of tetanus. The *length of illness* must also be considered: tuberculosis as against pneumonia. The likelihood of *complications and sequelae* must also be given due weight in evaluating morbidity. Poliomyelitis here would contrast strongly with chicken pox. Rheumatic fever would be weighted heavily both as to length of illness and as to complications and sequelae. *Potentialities for spread* of the disease under study is a factor to be considered in morbidity from acute communicable disease and potentialities of this sort are strongly manifested in such diseases as influenza and smallpox.

The third factor by which one may attempt to obtain some reflection of the public health seriousness of morbidity and mortality from a given cause relates to the age group in which that cause tends to focus itself. One encounters difficulty here in reaching a decision. From a biologic standpoint, and even sociologically, deaths in old persons do not constitute so serious a loss as would arise from the same number of deaths in young adults. However, an attempt to express this loss mathematically opens up many pitfalls. Thus, it has been suggested that biological and social loss in deaths be expressed in terms of the loss of life expectancy entailed. According to this concept, there would be entailed in the death of 100 persons at the age of fifty the loss of some 2,300 life expectancy years,

inasmuch as expectancy at the age of fifty is twenty-three. Similarly, 100 deaths at the age of twenty-five would entail the loss of some 4,400 life expectancy years. One might coldbloodedly accept this as a pretty good formula and say that a disease that focuses its effects in the third decade of life is, other things being equal, about twice as serious as one affecting those in the sixth decade. But if such a measurement were accepted, very serious collateral difficulties would arise, for while it is true that the number of years which the average person of fifty may expect to live is twenty-three, this is a general figure. For females, life expectancy at fifty is twenty-five years, males, only twenty-two. Therefore, if one observed such a formula blindly, it would inevitably follow that at any given age the saving of females would take precedence over the saving of males; and inasmuch as the non-white expectancy at a given age is considerably shorter than that of the white, another impossible sociological choice would be presented.

In assaying the relative seriousness of morbidity at the various ages, one can be somewhat more impersonal though not necessarily more accurate in evaluation. Obviously, there is a greater economic loss in the illness of one gainfully employed than in one too old to work. Similarly, the illness of a child entails a less serious economic loss than that of an adult, unless a gainfully employed adult must give care. Further, while the focusing of first attack in children may not entail an immediate serious economic loss, the likelihood of crippling after-effects in adulthood must be considered. However, in spite of all inherent difficulties in evaluating illness and deaths in terms of age affected, one can proceed fairly safely on the general thesis that morbidity and mortality exerted on children and on the young adult group, is more serious than when focused on older groups, the members



of which have already made their biological and sociological contributions.

As mentioned above, the relative seriousness of a given public health problem is not necessarily reflected in the practice of the typical health agency. Logically, between seriousness of problem and exercise of control measures, there should be a constant ratio. Because this is not the case, it would seem desirable to determine just what influences, quite apart from the seriousness of a given problem, operate in shaping the pattern of public health practice. It would appear that these factors come under one or more of the following headings: (1) the relative amount of scientific knowledge available for the prevention or control of a given disease, (2) the applicability of this scientific knowledge, (3) legal requirements and prohibitions, and (4) public interest and support. Each of these needs further exploration.

As regards availability of scientific knowledge, it may be said that if there is scant knowledge as to how a disease may be prevented or controlled, the activities of the medical profession, the health agencies and the public are not likely to be productive. The health department may proceed empirically and hope for the best, and may make certain gestures under the pressure of legal requirements and public opinion. But if these requirements and pressures do not exist, a health department will ordinarily be most active in relation to those diseases in which clean-cut control measures are available, and least active in those in which scientific knowledge is meager; and this, to a great extent, regardless of the seriousness of the disease in comparison to other diseases.

As to the prevention and control of a given disease, even when scientific knowledge is available there may exist circumstances that interfere with the application of that knowledge. Thus, in certain com-

municable diseases, *foci may be so disseminated* and masked as to make their discovery and control impossible. This is particularly the case in some of the upper respiratory infections, and in some instances in which animals or insects serve as reservoirs. Another deterrent to application of control measures is that their effective application might invoke a *stringency of action incompatible with the legal rights or freedom of action* of individuals affected. It is, for instance, legally and from a practical standpoint impossible to isolate each person with a cold; and if some fervid anti-vivisectionist caught diphtheria and refused antitoxin because it comes from the blood of a horse, that person could not be forced to take antitoxin. The *cost of an undertaking* might interfere with the application of knowledge. This type of limitation may be illustrated by citing problems in hospitalization or in elimination of malaria through mosquito control.

An *unfavorable attitude by the medical profession* might serve, temporarily, as a deterrent in the application of new knowledge. This is seen occasionally when the health department, acting as an agency of government, undertakes control measures that a local medical profession regards as sociologically objectionable. This occurs most often in the operation of clinics of one sort or another and in medical care of individuals. *Legal requirements* may be such as to force a health department to continue outmoded procedures, or *legal authority might be wanting* for the carrying out of certain obviously desirable procedures. It must never be forgotten that an official health agency must work within the legal framework of the government of which it form as part, and any given health department program must reflect this association.

The discussion of influences that shape public health work, of both official and voluntary agencies, comes finally to a con-

sideration of *public opinion*. One immersed in scientific problems might be inclined to brush this aside as having no bearing on the matter; he might even become exasperated because so unscientific a thing as public opinion is brought into consideration. But regardless of how ill founded the public's opinion might be on one aspect or another of medical and health matters, that opinion, whatever it is, has a very marked influence on the kind and the amount of public health work that is done. Also important to bear in mind in this connection is the fact that public opinion is the net outcome of the interaction of a great many forces and influences. It is, therefore, the part of wisdom to try to discover why the public thinks as it does and how one may best obtain public support for research and practice in any given activity designed to develop new knowledge and better measures for the control of any given disease.

Now, if one applies to rheumatic fever the various criteria that might reflect partly its public health importance, and further inquires as to its present position in public health practice, the results are somewhat disquieting. While an audience such as this is quite familiar with mortality and morbidity data of rheumatic fever, it might still be profitable to restate certain figures that put mortality from rheumatic fever in comparison with deaths from some other causes. Three causes of death with which deaths from rheumatic fever are compared loom large in public health activities: diphtheria, whooping cough and poliomyelitis. From data for the United States in the year 1944 (Table 1), which year was fairly typical, it is found that from all causes there was a total of 1,411,338 deaths: 1,878 of these were caused by whooping cough, 1,145 by diphtheria, 1,361 by poliomyelitis and 27,010 as a part of the rheumatic fever chain of events. When expressed in relation to population, the following mortality rates

are derived: whooping cough, 1.4 deaths per 100,000 population; diphtheria, 0.9 per 100,000; poliomyelitis, 1.0; rheumatic fever, 20.4.

Viewed in terms of proportionate mortality, it is found that whooping cough caused 0.1 per cent of all deaths; diphtheria, 0.1 per cent; poliomyelitis, 0.1 per cent; and rheumatic fever, 1.9 per cent.

But these are overall rates and proportions and it is always possible that such crude data may mask important details. Data could be broken down into age, sex, race, geographic locale, economic circumstances, etc. For present purposes no further detail will be undertaken than a separation of deaths under twenty years of age and twenty years of age and older. Proceeding thus, it is found that of deaths from all causes in persons under twenty years of age, whooping cough caused 1,872 or 1.1 per cent; diphtheria, 1,057 or 0.6 per cent; poliomyelitis, 965 or 0.6 per cent, and rheumatic fever 2,248 or 1.3 per cent. Perhaps somewhat easier for comparison are the mortalities from these four diseases expressed as rates specific for the under-twenty group. Whooping cough has an age specific mortality rate of 4.1 death per 100,000 persons aged 0-19; diphtheria, 2.3 per 100,000; poliomyelitis, 2.1 per 100,000 and rheumatic fever 4.9 per 100,000. Expressing somewhat differently the mortality experience with these four diseases in the age group twenty years of age and over, it may be said that for each death caused by whooping cough, diphtheria and poliomyelitis combined, there are about fifty deaths from rheumatic heart disease.

One could go much further in analysis and comparison of mortality from rheumatic fever and other causes, as pneumonia, tuberculosis, cancer, etc., but even from the above and limited consideration, it would seem safe to say that mortality from rheumatic fever is sufficiently great, both com-

TABLE I  
DEATHS FROM ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE  
AND FROM CERTAIN OTHER CAUSES,  
PER CENT OF DEATHS FROM ALL CAUSES, 1944, U.S.,  
AND AGE SPECIFIC DEATH RATES

Age Groups	Deaths*						Per Cent of All Causes					Age Specific Death Rates				
	All Causes	Rheu. Heart Dis.	Polio-myelitis	Diphtheria	Per-tussis	TBC (all)	Rheu. Heart Dis.	Polio-myelitis	Diphtheria	Per-tussis	TBC	Rheu. Heart Dis.	Polio-myelitis	Diphtheria	Per-tussis	TBC
0-9	144,930	655	495	988	1,867	1,892	0.5	0.3	0.7	1.3	1.3	2.8	2.1	4.1	7.8	7.9
10-19	27,491	1,593	470	69	5	2,994	5.8	1.7	0.3	...	10.9	7.2	2.1	0.3	...	13.6
20-29	49,762	1,678	192	23	2	9,715	3.4	0.4	...	...	19.5	8.5	1.0	0.1	...	49.3
30-39	67,465	2,480	120	22	1	9,899	3.7	0.2	...	...	14.7	12.4	0.6	0.1	...	49.5
40-49	116,827	3,346	45	12	1	9,557	2.9	...	...	...	8.2	19.0	0.3	0.1	...	54.3
50 and over	1,004,863	17,258	39	31	2	20,674	1.7	...	...	...	2.1	58.7	0.1	0.1	...	70.3
Total...	1,411,338	27,010	1,361	1,145	1,878	54,731	1.9	0.1	0.1	0.1	3.9	20.4	1.0	0.9	1.4	41.3

Data taken from Vital Statistics of the U.S., 1944, Part 1.  
\* Corresponding to the following titles of the International List of Causes of Death:  
Rheumatic Heart Disease: 58, 90a, 92b, 92c, 93c, 95b  
Poliomyelitis: 36  
Diphtheria: 10  
Pertussis: 9  
TBC: 13-22  
—: less than 0.05% or less than 0.05 per 100,000.

paratively and absolutely, to indicate beyond doubt that it constitutes one of the very serious public health problems. Additional details may be gotten from Table I.

But the importance of the problem looms even larger when to mortality there is added the burden of morbidity. Time forbids a detailed comparison of length of disability, economic loss and case fatality from rheumatic fever and from other diseases. Further, morbidity data are not as complete or accurate in rheumatic fever, which is not generally a reportable disease, as in those that are reportable. However, reasonably careful sampling observations suggest strongly that only a few diseases are comparable to rheumatic fever, either in number of cases or in terms of disability, in childhood and in the productive period of life. The disease must, therefore, be weighed heavily in relation to morbidity. However, in spite of these conclusions, measures for prevention, control and care of cases of rheumatic fever occupy only a minor rôle in the health activities of most communities.

In light of the previous discussion of the

influences that tend to shape public health programs, what might be the reasons for this seeming neglect? These, it would seem, are not difficult to discover. They are presented, not in endorsement of the situation, but as an analysis of it. In the first place, there is only limited scientific knowledge as to prevention and control of rheumatic fever in the individual or the mass. There is no vaccine or clear cut measure for prevention; there is neither specific therapy to ensure recovery nor any uncomplex procedure to prevent recurring episodes. The next problem is that such measures as are available for treatment involve a somewhat specialized medical skill and rather costly hospitalization. If what is generally believed to be the rôle of the streptococcus in precipitating initial and recurrent attacks (regardless of the question of familial susceptibility) is correct, then the disease falls into the category of one of those with a vast number of undiscoverable and uncontrollable foci.

These are some of the factors that have served as deterrents to more widespread and

intensive work on rheumatic fever in community health programs. But there is another factor which strongly influences the situation. This is that, heretofore, the public interest has not been aroused. Again, it is not difficult to determine why. There is nothing in the disease that, without careful public health education, would appeal dramatically to the public. Perhaps if all cases of rheumatic fever manifested severe clonic spasms, as sometimes seen in chorea, the public would be more impressed; as it is, the damaged heart is beyond public recognition. Not only this, but such overt disturbances as the sufferer might have, occur in the seclusion of his home or at the hospital. All in all then, everything has been against public interest and support of measures for research and control of rheumatic heart disease.

Nevertheless, public interest is an immediate necessity, a first step, if this disease is to be given that attention which its seriousness demands. New knowledge and more productive control and care must, to a considerable extent, wait upon adequate funds; adequate funds, both for voluntary and official health agencies, must wait upon greater public interest and support.

Viewing rheumatic fever in perspective with other public health problems, it seems sound to conclude that quantitatively and qualitatively, it is one of the most serious; that it does not receive from society or society's health agencies an amount of attention comparable to its importance; that the public's interest and support, both directly and indirectly, is not likely to be aroused without the very careful development and maintenance of a program of health education and publicity, nation-wide in coverage, and under the expert guidance of professionals in the field of public relations.

#### DISCUSSION

DR. QUINN (*New Haven*): Among the diseases that you have mentioned, particularly

diphtheria, whooping cough and poliomyelitis, the diagnosis from the clinical standpoint is relatively easy to make. On the other hand, the diagnosis of rheumatic fever is often a difficult matter. Thus in the latter disease, many cases may have been missed and on the other hand, many have been overdiagnosed. On this basis, do you think that the figures that you have given us are comparable?

DR. MUSTARD: I think you are quite right in the statement that rheumatic fever, unless in a dramatic form, is much more likely to be overlooked than whooping cough in its typical manifestations or diphtheria. That would not apply to the subclinical attack of poliomyelitis. We miss a great many of those.

The best data that one can find on relative incidence of rheumatic fever are therefore those that come from the studies made by authorities in that field. Even then we do not have a good population to put these data against.

It is obvious, of course, that it is much more difficult for a general practitioner to make a correct diagnosis than it would be for those who are managing rheumatic fever in an institution like this.

MISS CULLEN: Have any errors been committed in the type and character of education that we have been conducting for the public in the matter of rheumatic fever? It has been said that if the interest of the public is to be aroused in a disease, one must be prepared to offer to the public measures for its management and control. Since we do not have such ready-made methods and since we do not even have sufficient facilities for the care of this acute illness, have we a right to raise the question before the public eye? Is it not true that a great many misconceptions may be transmitted to the public which might create neuroses?

DR. MUSTARD: We are, of course, getting into a difficult field when we attempt to measure the value and harm of education.

I remember once I was up before an appropriating body in a rural area trying to get some money for public health work. There were fifty-two rural magistrates present. One of them seriously jeopardized the situation by expressing the opinion that the country had already been nearly ruined by too much good roads and education. He carried this conviction and prejudice into the field of public health. But I think I understand the basis of your question. When we emphasize to the public the seriousness of a disease and paint a gloomy picture as to what might happen here or there, we are faced with the danger of doing serious psychological injury to the individual who is involved. We must strike a nice balance lest we impose, in addition to his physical disease, some mental distress and handicap.

I do believe, however, that with carefully worked out health education programs, there can be developed, without injury to any one, public understanding and monetary support of public health activities in rheumatic fever.

DR. TARAN: May I qualify the question? It has been said repeatedly that the public may be taken into confidence about disease only to bring the public to the support of the combat of the disease. However, to take the public into confidence as to the severity or the symptomatology of the disease may be very dangerous. This form of propaganda has been tried in rheumatic fever from the point of view of bringing more cases to the clinic, bringing more cases to the doctor somewhat analogous to the campaign for cancer. Thus various brochures and public statements have been made dealing with the symptoms of rheumatic disease. Are we now in a position, with the knowledge that we have about rheumatic disease, to take the public into confidence as to the type of a disease it is?

DR. MUSTARD: I think we should never undertake to develop in the public any

responsibility or proficiency in diagnosis. To do so would lead to endless difficulties, apprehensions and disasters. That has been tried, particularly in tuberculosis; and it has been done in cancer, and unfortunate situations have arisen. For instance, by the time that most people develop the advertised symptoms of cancer, they are already pretty far advanced cases. You will notice, too, that tuberculosis publicity is no longer concerned with the man with the thin chest, who is losing weight, who has a cough and spits blood. The emphasis now is that anybody might possibly have tuberculosis, even without symptoms. Generalities with enough punch in them to get action are quite practicable and are to be preferred to either a listing of diagnostic points or scare headlines that arouse the hypochondriac latent in most people. I agree with you that it is unwise to publicize diagnostic criteria.

MISS FEGLI: We have no adequate facilities for diagnosing rheumatic fever today, have we?

DR. MUSTARD: No.

MISS FEGLI: Nor have we adequate facilities for hospitalization of the patient. Under these circumstances, however, do you think we should go in for health education of parents of rheumatic patients?

DR. MUSTARD: I think so far as parents are concerned you should go just as far as you would if you had the facilities you need. I know you are going to question that by asking quite sensibly, "What is the use of getting them all stirred up about going to the hospital when there is no hospital for them to go to." Certainly one would have to adjust advice given parents to the local situation. On the other hand, I am convinced that if we limit our health education of the public in rheumatic fever to such an extent that the public itself does not feel the pressure or, rather, the absence of the facilities that it needs, that public is quite likely to remain smug in the belief that all is well.

It is my belief that the deficiency in community facilities should be emphasized and re-emphasized; and while I should certainly not want to get some mother all worked up about sending her child to the hospital and then be unable to do this, I think we can avoid those immediate situations with some tact. But it would be fatal for us to hold back our public emphasis on the seriousness of rheumatic fever until such time as we have facilities to meet the needs.

DR. QUINN: I would like to ask Dr. Mustard if he has the figures for tuberculosis for this same period in 1944, that is, the mortality figures.

DR. MUSTARD: To get a clear comparison here one must study detail. The total number of deaths reported due to tuberculosis is about twice those reported as caused by rheumatic fever and rheumatic heart disease. Further, if comparisons are made in wide age bands, as 0-19, 20-39, etc., tuberculosis rates will in each instance be greater than from rheumatic fever and this type of heart disease. However, there is one age band in which mortality from rheumatic fever and its associated heart condition is greater than from tuberculosis. This is the group aged five through fourteen years. The respective age specific mortality rates in this ten-year period were 5.7 and 3.8 per 100,000 population in 1944.

#### SUMMARY

DR. TARAN: Rheumatic fever was discussed in the perspective of public health. It was pointed out that the obvious criteria

which shape public health practice are mortality, morbidity and the age group in which morbidity and mortality tend to focus themselves. Applying these criteria to rheumatic fever and rheumatic heart disease, this disease becomes evident as a most burdensome public health problem. Factors which shape public health practice in rheumatic fever as in other diseases were described in detail. The relatively scant scientific knowledge available for the prevention or control of the disease, the difficulties in applying scientific knowledge at hand, legal-sociologic deterrents and prohibitions and lack of public interest and support may be factors responsible for influencing the official and voluntary public agencies from mobilization of their forces in the combat of rheumatic disease. Yet, viewing rheumatic fever in perspective with other public health problems, it was concluded that quantitatively and qualitatively it is one of the most serious; that it does not receive from society attention comparable to its importance; that the public's interest and support is not likely to be aroused without a careful development and maintenance of a program of health education and publicity nation wide in coverage under the expert guidance of professionals in the field of public relations. The education of the public must guard against the creation of hysteria. The aim is to develop in the public not proficiency in diagnosis of rheumatic disease, but rather an understanding of the measures which are necessary to control this illness.

# The Rôle of the Medical Social Worker in the Management and Control of Rheumatic Fever and Rheumatic Heart Disease<sup>\*</sup>

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NEW YORK, NEW YORK

THE rôle of the medical social worker in the management and control of rheumatic fever and rheumatic heart disease can be most clearly described in terms of five activities or functions: (1) Case work services to individual patients and their families; (2) participation in patient management and clinic administration; (3) participation in the development of community resources; (4) medical social research and (5) participation in the teaching of professional personnel.

All of these are important activities through which a distinct and unique contribution to a total program can be made by medical social personnel who are skilled in observing and evaluating social data and are also skilled in relating social and medical data.

It is regrettable that in the field of social work we have been unable to provide such skilled personnel in all of the positions which need qualified workers. The inability of the field to make such provision has led to confusion as to appropriate activity of the social worker, to partially effective social service in many places, and to serious gaps in programs in other places. In this paper I am referring to the rôle and contribution of the skilled medical social worker.

*Some Social Aspects of Significance.* Before discussing the activities of the social worker

in a program for the management and control of the specific diseases of interest to this group, there is value in reviewing some of the aspects of the diseases and the care of patients which have particular social significance. Although both diseases are indeed medical conditions and primary responsibility for prevention, control and care of patients rests on physicians and medical agencies; the social component is significant and substantial responsibility for prevention, control and care of patients rests also on social workers and social agencies. Such responsibility can be demonstrated by four points:

1. Although the specific cause of rheumatic fever has not been discovered, it is agreed that there is an individual susceptibility and that rheumatic fever is more common in some families than others. What emotional and environmental factors are in these two facts about susceptibility is not clear. What is of social significance is that it is also agreed that factors which favor onset and recurrence in the susceptible individual are frequent chilling, damp or overcrowded living quarters, poor diet and conditions leading to lowered resistance.

2. Rheumatic fever is serious because it may affect the heart. Attacks tend to recur and repeated attacks are more likely to damage the heart. If the heart is only slightly

<sup>\*</sup> One of the Seminars on Rheumatic Fever given at the St. Francis Sanatorium for Cardiac Children, Roslyn Long Island, N. Y.

† From the New York School of Social Work, Columbia University, New York, N. Y.

damaged, the patient may be able to live a normal life; but if the heart is seriously impaired, his activity will be markedly curtailed. Unless recurrences can be prevented, some of the patients will be handicapped persons whose social adjustments, school, employment, family life and personal life are seriously affected. While it is true that physically handicapped individuals can have a wholesome interest in life and enjoy many of the activities of their associates, handicapped individuals frequently need special help in accepting the handicap, in adjusting to it and in choosing activities which are satisfying and in accord with the limitations imposed on the individual.

3. There is no medicine that will cure rheumatic fever although some help, but the treatment during the acute phase and for several months is rest in bed. Rest in bed raises the problem of community resources and personal problems of the individual and family. In only parts of this country are facilities in hospitals available for treatment of the relatively short acute phase of the disease, but in no part of the country are there adequate provisions for the number of patients needing longer periods of bed care, nor for the prolonged periods of convalescence. From the medical point of view, special institutions or sanitariums are considered essential for some patients and desirable for most convalescents. Only in such institutions can the regimen of the patients be as carefully controlled as is deemed wise to protect the heart and avoid such dangers as upper respiratory infections. Such institutions could approach the ideal from the physical standpoint; but from the social standpoint, the continued isolation of the patient from his home and family, the dependence upon others to select his activities for him, the secondary rôle played by parents, the problem of helping the patient and family to readjust to each other and to

accept responsibility for the recommended regimen after a year or two of controlled environment are aspects of the management program which have major social and emotional significance.

4. Continued supervision by periodic medical examination is recommended for an indefinite period, with effort made to have the patient return at least once in six months, even though symptom-free. Prolonged and detailed observations are considered necessary in studying the natural history of heart diseases. Also such supervision is considered essential because of the importance of early recognition of the signs of possible renewed activity of rheumatic fever, for continued education of the patient and because of the importance of medical advice on the increase of activity after a period of demonstrated tolerance. This continued medical supervision over a period of years has good psychological as well as physiological effects for many patients, but for some continued supervision is intolerable. For others, the continued medical observation gives tacit proof that they are still ill regardless of what the doctors say and the continued surveillance may arouse anxiety and fear which may result in time in cardiac neurosis and excessive introspection. The prolonged medical supervision which has only positive aims, one of which is to prevent a damaged heart if possible, may be a contributing factor in the making of a cardiac invalid.

These and other social aspects are recognized as existent by medical, nursing and social personnel who work with patients with rheumatic fever and rheumatic heart disease; they are the particular problems of concern to the medical social worker. It is in respect to problems such as these that skilled social service is needed if the program of management and control is to reach its objectives. The use of social work in these programs is described by repre-



sentative persons whom I wish to quote. Dr. Huse, special consultant in Medical Services, U. S. Children's Bureau, wrote with regard to acceptance of the diagnosis and recommendations by the child and his parent: "The medical social worker or the public health nurse or someone else in whom the parents have confidence, such as the priest, may be called on to help interpret the situation to the family. . . . A thorough knowledge of the family situation and great patience and skill in dealing with the difficulties are necessary in order to deal with this type of situation. The State medical social workers have had to deal with many such cases, using not only their own skills but also many sources of information and help within the community."\*

In a pamphlet describing state programs for care of children with rheumatic fever, medical social services are described as follows: "The medical-social consultant on the State agency staff is responsible for seeing that any family and environmental difficulties, or the feelings of the child about his condition do not prevent him from following the treatment recommended or getting maximum benefit from this treatment. The medical-social consultant becomes familiar with the needs of individual children in many ways, such as by talking with them and their families in the clinic, during hospital and sanatorial care and at home when necessary. In order to meet these needs, the medical-social consultant helps community social agencies understand the kinds of problems that interfere with adequate care of the child and helps to stimulate development and improvement of the necessary services."†

In a small pamphlet, "Rheumatic Heart Disease in Children," published by the

\* HUSE, BETTY. If a child has heart disease or rheumatic fever. *The Child*, pp. 163-165, May, 1944.

† U. S. CHILDREN'S BUREAU. State Programs for Care of Children with Rheumatic Fever under the Social Security Act. 1944.

American Heart Association, Dr. Bland writes in a section on treatment, with reference to prolonged bed care and convalescent care, "There are few institutions for this special purpose at the present time and more are needed, but until then much can be accomplished by special heart clinics in our general hospitals. The major part of the work falls upon social service and charitable organizations under the direction of out-patient clinics and interested physicians. In this way satisfactory convalescent care has been arranged for many patients in their own homes, and for others in special foster homes. Not only has it been possible to provide this necessary bed care, but valuable service also has been rendered in making certain that the instructions of physicians are understood by the patient and the family, in securing the cooperation with school authorities for home teaching and special vocational guidance; finally, with the aid of capable volunteer workers, in maintaining the morale of these youthful patients at a surprisingly high level in spite of months in bed in uninteresting surroundings. Such service requires and deserves the interest and support of every community."

The New York Heart Association in its publication, "Standard Requirements for a Cardiac Clinic,"\* includes these statements:

#### "SOCIAL SERVICE

"The following outline is not intended to list all the responsibilities of a cardiac social worker, and includes only those duties indispensable to the operation of the clinic.

#### "Major Objectives†

"The major objectives recognized so far as appropriate to hospital social service are:

"Inquiry into the social situation of . . .

\* Published 1936 by New York Tuberculosis and Heart Association, Inc.

† From The Functions of Hospital Social Service Monograph No. 1 of the American Association of Medical Social Workers, pages 62-63.

patients and the reporting of the findings to the responsible physician . . .

"Determining, in collaboration with the physician, the factors in the social situation pertinent to the patient's health . . .

"Setting up, in collaboration with the physician, a possible goal . . . for the patient . . .

"Executing the social worker's part in the plan for helping the patient . . .

#### "Responsibilities

"The social worker shall be present during the entire clinic session and should interview all new patients on their initial visit, and all return patients as necessity demands.

"The social worker shall supervise the return appointments to the clinic, shall keep a record of the visits of individual patients, and shall follow all patients who fail to keep their appointments.

"Patients who have not returned to the clinic for a period of six months since the date of their return appointment shall be visited before being transferred to the inactive list.

"Home visits should be made on all new patients as soon as possible, and the Social Record (No. 4 of the New York Heart Association forms) should be completed not later than three weeks after enrollment.\*

"On order of the physician, the social worker shall arrange for the hospitalization or convalescent care of patients.

"The social worker shall be responsible for the transmission of reports concerning cardiac patients to school nurses, visiting nurses, and other social workers.

"When patients are transferred to another clinic or institution, the social worker shall be responsible for sending a transcript of the record.

"The cardiac social worker shall keep a record of active and inactive patients, clinic attendance, readmissions, and social service visits. These records shall conform to the schedules devised by the Committee on Cardiac Clinics, and should be submitted every month to its Execu-

\* In order to establish a diagnosis a patient is sometimes required to make three consecutive visits to the clinic. In clinics holding weekly sessions, the final diagnosis may not be established until the third week.

tive Secretary. (A sample of these schedules may be secured from the Executive Secretary of the Committee on Cardiac Clinics.)"

These citations from writings which present the problems of rheumatic fever and rheumatic heart disease and the broad programs for care do not make clear, in most instances, the actual services of the social worker. They suggest the general rôle that is played. In the statement of standards by the New York Heart Association, the specific responsibilities in relation to patient management and record keeping are detailed as the statement purports to give only "those duties indispensable to the operation of the clinic." As might be expected, one finds detailed descriptions of the medical social worker's activity in articles written by social workers.\*

#### CASEWORK SERVICES TO THE INDIVIDUAL PATIENT AND HIS FAMILY

Social casework has been variously defined; there are many gradations in its practice. Casework is not synonymous with social work; it is one of the processes used in social work. Stated in terms of process, medical social casework in a cardiac clinic is essentially this: From the doctor the caseworker secures the medical data and the doctor's understanding of the patient and his problem. Through interviews with the patient and possibly one or more members of the family, the caseworker learns much about the patient as an individual—his personality, his social situation, his family relationships, his understanding of his medical condition and his attitudes toward his illness and medical care and toward the limitations which are imposed

\* EBERT, VIRGINIA. Case work services to children with rheumatic heart disease. *The Family*, pp. 7-14, March, 1941. COHEN, ETHEL. The social component in heart disease. *Am. Heart J.*, pp. 422-430. October, 1938. TERRY, EDITH. Some social aspects of rheumatic heart disease. A paper given in 1940 in a symposium on Rheumatic Fever and reproduced for distribution by the New York Tuberculosis and Health Association.

on his activity. Through contact with others who know the patient or the family situation, such as social agencies, school teachers and nurses, she may supplement her observations and information and thus gain more understanding of the person and his social situation. The evaluation and analysis of data constitute a diagnostic process which is most effectively done when collaboration with the doctor is possible. The doctor who has examined and studied the patient as an individual with a medical condition and the caseworker pool their findings and their evaluations of their data and together they arrive at a medical social diagnosis. There is value not only in pooling findings and arriving at an accurate medical social diagnosis, but also in joint thinking regarding recommendations to the patient and in sharing treatment plans, at least to the extent that each will understand the part the other is playing in the care of the patient. The caseworker continues study of the patient, just as does the doctor, as treatment progresses. The basis of casework treatment is the establishment of a relationship with the patient (or the parent) that will enable the caseworker to be helpful to the patient in meeting his needs. Through interviews and through mobilization of community resources, if needed, the caseworker continues her service to the patient as long as her services are useful to him or his family. Casework requires professional skill; it frequently requires a substantial amount of time for intensive study and treatment; it is the major activity of most medical social workers in hospitals and clinics.

The content and value of casework can be illustrated better by a case situation than by a description of it as a process:

Jack Martin, aged fourteen, was admitted to the hospital through Emergency Service. The boy had joint pains, a sore throat and a fever of 103°F. Subacute bacterial endocarditis was considered as a possibility but ruled out,

and a diagnosis of acute rheumatic fever was made.

*Past Medical History.* Jack had been under the care of a private physician intermittently for the past seven years. His first attack of rheumatic fever had occurred when he was seven years of age. He was bed fast for a year, but by the time he was nine years old he was up and about all day. However, he got joint pains when he attempted to go to school so he lived on a fairly restricted program of home study and quiet play activities. At the age of twelve, he had returned to school, but a few months later he had a second attack of rheumatic fever, less severe than the first but necessitating bed rest for six months. Gradually he increased his activities, but did not return to school. He believed his present symptoms were due to over-exertion, as he was playing basket ball quite steadily for several days before he came to the hospital. He realized this was too strenuous for him but thought he would like to try an active sport for a while.

*Medical Care.* Jack was kept in the hospital seven weeks, on complete bed rest, before his mother asked to have him discharged against medical advice.

*Social data* were secured from the mother and patient while the patient was on the ward.

The patient was a dull looking, blond boy whose response was very slow. It seemed as though he did not hear very well because it was always necessary to repeat statements. When the worker introduced herself to the patient on the first occasion, his reply was, "I can't talk about my family. I always put my foot in it. My mother likes to do that and will tell you anything you want to know." He expressed very little interest in the things around him and was quiet. He did express a desire to become a radio mechanic and for that reason was anxious to get well. When occupational therapy was recommended by the doctors, the patient said that he did not think he would like it and that he would prefer not having anything to do. He was not demanding or uncooperative on the ward.

*Habits.* He usually stayed in the house reading or working on the radio with which he liked to experiment. Usually his activities were re-

stricted to no strenuous sport, but this summer he had participated in basket ball games. At school he was greatly retarded and was not very quick. He had no particular interest in school but was anxious to finish as he wanted to be a radio engineer.

*Food Habits.* According to the patient and his mother he was on a diet but upon inquiry it was learned that the patient's diet consisted of the foods he liked with the elimination of all the food which he disliked. His favorite meal was a toasted cheese sandwich. The mother had little or no conception of a well balanced diet and had allowed her son to let his food fancies develop to such an extent that his food habits were very poor.

*Environment.* The patient, his mother and one older brother occupied a four-room apartment on the third floor of a walk-up apartment. The mother stated that it was not a very nice apartment but it was the best that she could afford.

*Finances.* The income of the family was paid to the patient's mother by the father and was \$17 to \$20 a week depending on the earnings derived from his trucking business. Because of the small income and the unemployment of the patient's two older brothers, they had left home and were living in the homes of the girls whom they expected to marry. Although the patient's mother did not approve of this, she shrugged her shoulders and said there was nothing she could do about it.

*Family Relationships.* The patient had a very definite place in the family group and was treated by them in rather an unwise way. His differences from the rest of the family were stressed rather than his assets. There was some question as to how much the patient and his mother were able to understand about his condition. For the past few months the patient's father had not been living in the home and, according to the mother, was not interested in the patient's welfare or in any one else's welfare.

*Marital Relationship.* According to the patient's mother she and her husband had never gotten along very well and he had always gone with other women and had had several children by them. She showed the worker a letter received from one of these women when she was in the

hospital having just given birth to a child of his. The patient's mother stated that she was worried because her husband had told her that he was planning to divorce her in order to marry a young girl who was about to become a mother. If he divorced his wife, she did not know how they would get along because he did not earn enough to support two families and she had no other source of income.

*Atmosphere of the Home.* It was evident that the home situation was not satisfactory and there was some question as to whether or not this would interfere with the carrying out of the patient's treatment. Evidently the patient's mother discussed the marital situation with the patient at great length and he was familiar with the marital difficulties she had had.

*Patient's Mother.* The patient's mother was an uneducated woman who had very little idea about looking after her children although she did express interest in the patient. She delighted in talking about the unfaithfulness of her husband and considered herself very brave in putting up with all of his wanderings. She was oversolicitous about the patient.

*Social Service Exchange.* No record.

*Social Worker's Impression.* It was believed that the patient may be helped in making his adjustment to his handicap and in understanding his illness. The marital situation had existed in the family for such a long time that it was doubtful if any one from the outside could assist in a solution.

Regrettably, the next notation in the social record is not a statement of case work treatment over a period of seven weeks, but a statement regarding the patient's discharge from the ward:

*Discharge Note.* Patient's mother preferred to take him home although he should remain here. She believed she could treat him better at home. She had recently moved to an elevator apartment, where the patient would be able to get up on the roof.

The social data noted in the record meets the requirement of a social history as part of a medical study. It does not give evidence

that the social worker carried on any continuous contact with the patient or his mother during this critical period. It does not give evidence of development of a relationship with the boy which make casework treatment possible.

The next entry is seven weeks later, made after a follow-up visit had been made by another worker from the social service department, maybe by a person who was assigned to make follow-up visits. Her entry is as follows:

*Home Visit.* Because the patient had not returned to the follow-up clinic, a visit was made to the home. The patient's mother had been giving him most devoted care although it had been difficult for her to make the patient obey. The patient's mother was carrying out her own theories of medicine and medical care and stated that she would not bring the patient into the hospital unless the doctors agreed to carry out her recommendations. In addition, although she believed that the doctors knew what was wrong with the patient, she did not believe that they knew how to treat his illness. She had planned to take the patient to another hospital but he had been too weak to be moved. He was running a temperature in spite of the efforts of his mother to bring it down by depriving him of such foods as she believed cause fever. If the patient were readmitted to the hospital, very definitely his mother would be a problem because she would want her ideas about food and care to be carried out on the ward. The patient received good care at home and if the mother was unwilling to bring him back to the hospital it seemed that the best solution to the problem was for him to remain at home.

In a sense, another requirement of a program of management and control had been met: a follow-up visit was made and recorded. The reason for his failure to return is now known. The mother did not want to continue the patient's care in that hospital. That is clear, but what is also clear is that this boy and his mother were not able to handle the boy's illness nor any of his prob-

lems in a way beneficial to the boy. Casework treatment was indicated as well as further medical care. Neither was received; instead the boy was placed eventually on the inactive list, with a notation, "Mother prefers care elsewhere." This case record started with adequate medical and social study, but the mother rejected the medical treatment and social casework treatment was apparently not offered. The social history and the follow-up visit in the home do not appear to have been helpful to the patient, to the mother nor to the physician.

Five years later Jack appeared in the clinic. Thus a three-year period of active medical care and casework treatment was begun.

Jack, now nineteen, was underdeveloped and appeared listless. His complaints were frequent colds and a discharging ear. He had not had any more acute attacks of rheumatic fever since he left the hospital against advice five years before. He had gradually resumed activity but at no time had he felt able to return to school. He stated that his usual program consisted of arising about mid-morning, putting about the house until his home teacher came in the early afternoon, reading and tinkering with his radio in the evening. He seldom went out of the house for more than an hour, usually for a short walk in the neighborhood. He had taken cod liver oil and a tonic when his mother could afford it. His appetite was poor and sometimes he was unable to sleep and read half the night. He sometimes went to the park and to the movie but he "mostly stayed in the house." He had not attempted any sports. "His mother took good care of him," insisting on his remaining in bed when he had a cold. "She fussed when he didn't eat well."

*Physical Improvement.* Medical examination revealed that he had only slight heart damage. In the cardiac clinic, recommendations were made for gradual increase in activity. He reported faithfully for periodic checks for three years. Medical attention was centered on his continued upper respiratory infections and treatment of the discharging ear. He made

marked improvement in his general physical condition; when he was twenty-two he had been symptom free for a year. He had been employed in a sedentary job for six months.

*Social Casework Treatment. Patient's Response:* Jack was mildly interested in the worker's suggestion that she might be able to help him work out a program of increased activity as the cardiologist had suggested. He seemed doubtful that he could do much more than he was doing without getting sick again but he expressed discouragement over his progress in his studies. He wanted to "at least get beyond grade school." Gradually he became more talkative and interested in discussing how he felt about himself, his mother, and his activities. He was seen weekly for a few months, seldom missing an appointment. Gradually, appointments were lessened in frequency and during the third year of the contact he was seen only when he came to the hospital for his periodic exam in the cardiac clinic.

*Problems as Seen by Jack.* He was troubled over his learning speed. His teacher told him "he was intelligent" but he was discouraged. His mother, who was a "quick thinker" thought he was slow and criticized him for his lack of progress. His mother wanted him to be an office worker, but he wanted to be a musician. He thought he had a good voice and possibly could be a radio entertainer if he could afford music lessons. On the other hand, his mother could not afford music lessons, and anyway he thought he should do what his mother wanted him to do. He owed much to her; she had taken good care of him and he "ought to want to do as she wished—he owed her that much." He felt he was slow in everything. He did not believe he could get up in the morning and get to school, "even if a school with an elevator could be found." (The doctor had given permission for stairs and the patient still lived in a third-floor apartment.)

He felt he had to get to the place where he could support his mother soon; she had been "supporting him too long" on the small income from the father.

His mother urged him to eat heavily but he was afraid of "getting fat like his mother, although being overweight was all right for older

persons." He was "not unhappy at home all day." He had not "kept up with his friends" but "that was the way it was when you have a bad heart." He wanted to "make up for his illness somehow." This wish to "make up for his illness" seemed mostly centered toward making it up to his mother who had sacrificed so much to take care of him.

*Mother's Attitude.* His mother at first accompanied him to the clinic but gradually came less often and by the end of the year, Jack was coming to the clinic alone. She was an energetic, opinionated woman who continued to have definite ideas about Jack's treatment. She believed she knew better than anyone what diet he should have and what medicine he should be given. She prided herself on giving him the most expensive eggs, milk and chicken which were procurable. She talked about him as a child. She could not understand his confidence in the doctors as she did not have any, but he wanted to come. "She saved Jack's life five years before when the doctors gave up treatment for him." By dint of "hard nursing, she had brought him through." In his mother's presence, Jack sat slumped in his chair and failed to respond to her enthusiasm over his gain in weight. As Jack became more expressive about activity he wished to attempt outside the home, she became critical of his "independent notions," saying he "did not like her ideas any more."

*Personal and Social Progress.* Through regular interviews and establishment of relationship with both the mother and boy at first, then less often with the mother, the worker was able to help Jack try increased activities outside the home. He gradually began to take more responsibility for his own activity. He also began to wonder whether his colds were "mental." He liked to feel chilly and would sit by the open window or go outdoors without his coat unless his mother caught him. "She bundled him up too much." Gradually, he accepted more responsibility for dressing in accordance with the weather, without the nagging of his mother.

The worker arranged for him to have a voice test as part of the exploration for a vocational choice. On the basis of the test, Jack was willing to consider that music would be an avocation and lessons were arranged for at a settlement

house. Since he was too old to return to the public school to complete the eighth grade, a volunteer part-time teacher was secured to help him prepare for an examination for graduation from elementary school. After completing this period of study, the social worker helped him explore vocational possibilities and referred him to an agency which provided counselling, training and placement of the handicapped. He was given training in crafts and was later placed in a craft shop.

To find friends and undertake social activities was the hardest step for him to take. As he began to recognize that he was not really a "cardiac cripple," he was in conflict about social contacts. He realized that all his former friends and the boys in the neighborhood thought of him as having a bad heart and they had long ago stopped asking him to do anything with them. He felt "inexperienced" with boys of his own age and unwanted by younger boys. A series of community resources were used by the social worker in helping him find companions. Arrangements were made for attending a craft class at a settlement house; camp placement was secured for several summers at a camp that offered a wide program so that he did not feel the need to compete with the more active boys. He continued to be slow in accepting the doctor's recommendations for increased activity but after he had encouragement to try new things he expressed satisfaction in a more varied program.

While he was away at camp the summer he was twenty-one, his mother died suddenly of a stroke. The worker helped him adjust to this loss through close contact for a month. He was depressed over his loss and felt it was particularly hard to bear because the next month he was to begin his paid work at the craft shop. Feeling greatly indebted to her for her devotion of years, he also was somewhat relieved to be free of her growing dependence upon him. His brothers were all married and lived out of the city so his mother had concentrated all of her attention on him. He had considerable guilt over his sense of freedom, but was able to write his father that money need not be sent any longer as he had a job. The worker helped

him find a boarding house where two other young men lived.

At twenty-two he still had a slightly damaged heart and was a shy young man with only a start made in his social adjustments, but he was not the listless boy of nineteen who lived as a cardiac cripple.

#### DISCUSSION

DR. TARAN: Miss White's lucid and thoughtful presentation of the rôle of the social worker in the management of rheumatic disease is now open for discussion.

MISS BEGLEY (Nassau County Tbc. Assn.): In the management of the case which you presented, it would seem that the boy has been completely under the influence of the overattentive or "neurotic" mother. What rôle did the school authorities play in the management of this case? The case history gives me the feeling that the mother of this child needed psychiatric treatment as much as the child needed medical follow-up. Who would be responsible for the education or treatment of the mother of the child?

MISS WHITE: This boy was under the care of a private physician until he was fourteen; hence the hospital record does not have information as to the rôle the school authorities played. The nurse, school teacher or anyone coming into professional contact with the boy had a responsibility to size up the problem and to consider what help the mother could use.

MISS NEIL: Do you think that more visits on the part of the social worker before the patient became an adult would have changed the course of the disease?

MISS WHITE: The medical social worker, by making more home visits when the case was first known, could have offered more casework service. It is obvious that unless more detailed study is made in an individual case, the influence of the social worker upon the course of the disease will be small.

One home visit was made and the case

was closed. A person's interest in care cannot be definitely decided on one visit. I wish we would not be so quick with "closing a case." Unfortunately, this seems to be the present procedure in some places, possibly because of the great load of cases that the social worker carries. I do not believe in partial social workers' service any more than I believe in partial medical care.

MISS FITZSIMMONS (Long Island College Hospital): Do you think that the relationship of the social worker to convalescent homes and sanatoria should be closer than it is at present? It would seem to me that if the parents of the patient are to be prepared for the return of the child after he has sanatorium or convalescent care, that the social worker should be more closely acquainted with the progress of the case at the sanatorium or convalescent home.

MISS WHITE: Definitely. We cannot say that just because the patient has been transferred to an institution where the care may be excellent, the responsibility of the social worker in planning for the child has ceased. Possibilities for service by the social worker begin with the first acquaintance with the patient and continue throughout the course of his illness and as long as the patient may be followed. This is particularly true in a disease like rheumatic fever and rheumatic heart disease.

MISS DANZINGER: Is there a trend toward separation of casework and follow-up work?

MISS WHITE: I do not know of such a trend. The important question is one of use of personnel. We have to be practical in terms of distribution of responsibility among the available personnel. How are we to divide the time of a social worker between casework and follow-up? If a social worker makes fifteen follow-up home visits a month, there should be time not only for second follow-up visits if necessary, but time also for casework with those patients.

Unless the caseworker has time to carry on with casework treatment, the use of her time for follow-up is not only expensive but results in ineffective use of her skill. If follow-up visits are not to be supplemented by casework service, a clerk might as well be sent. It would seem that we had better do careful work on half as many cases, rather than to follow up many cases without casework service.

DR. TARAN: From the point of view of the social worker, where does the line of demarcation lie between the function of the social worker and the psychiatrist in the management of a rheumatic patient? We have now come to believe that rheumatic fever is a protracted disease of many years' duration, fluctuating between short explosive phases and long subacute protracted phases. The physician who is in charge of a case of rheumatic disease knows from the very onset of the disease that many sociologic and psychiatric problems will arise during the course of this patient's life, because of the protracted nature of this disease. For example, he knows that a child between six and twelve years of age who suffers from repeated recurrences of rheumatic fever will spend a good deal of time in the wards of hospitals, and will not therefore follow psychologically the normal childhood course of development. Both educational and psychologic problems arise during this period. The physician also knows that if this child develops severe cardiac damage he will be handicapped not only in his physical development but also in his sociological adaptations. When such a child has reached adult life, he will most likely be kept from the usual ways of earning a livelihood, and therefore develop rather profound emotional disturbances. The physician further recognizes that this rheumatic patient, if his cardiac damage is progressive and severe, will, in addition, develop a painful cardiac neurosis.



Many of these sociological and psychological disturbances can undoubtedly be modified when handled properly at the right time. What rôle does the social worker play and where does her work and the psychiatrist's work begin in modifying the course of events in the natural history of the disease?

MISS WHITE: I think that social workers come in at all of these stages, but with a different type of service than the psychiatrist. For example, when a child's life is threatened, medical treatment takes predominance over everything else. On the other hand, during the same period of time, the social worker may begin to develop a relationship with the patient upon which she can build later on. I believe that it is during this acute "medical" period that the social worker's job is to develop a proper relationship with the parents of the patient and perhaps also his siblings. We know that not only the patient will need assistance, when he recovers from the acute stage, but also attention to his immediate environment at home may be needed. When the patient gets ready to be mobilized into his social sphere, that is the time when the social worker can do much in helping him with these adjustments. When the patient develops emotional disturbances of a profound nature, the social worker must realize that this has become a psychiatric problem and encourage psychiatric treatment. I do not believe that many social workers are confused as to where our work ends and the psychiatrist's work begins. When the social worker does not realize where her function ends and the psychiatrist's begins, her training is deficient.

It must be admitted that from time to time, the social worker invades the territory of the doctor, the nurse or the psychiatrist. This is done not because she does not realize her function nor because she ignores the value of the nursing or psychiatric

services, but simply because of the fact that many programs are inadequately staffed. The tendency to do each other's job is of necessity, rather than choice. If a social worker must fill the gap for the doctor, nurse or psychiatrist, at least she must keep clear in her mind what she is doing and why. If we do that, there will be less confusion. I am convinced that from time to time it is a good plan for physician, nurse, social worker and psychiatrist to get together and to pool and coordinate their thinking. Until the personnel problems are solved, there will be a great deal of overlapping and filling in for each other.

DR. TARAN: I remember a statement by Dr. L. F. Barker at one of the meetings of the Academy of Medicine. He said that he thought that prevention of rheumatic fever was impossible because there was no clear demarcation between the function of the doctor, the nurse and the social worker. He cited the following example: The doctor stated that one way to prevent rheumatic fever is to avoid chilling, and the way to prevent chilling is to wear an overcoat and rubbers. In this instance, the patient was a boy who did not like to wear an overcoat and rubbers. The nurse was sent out to insist that the rubbers and overcoat be put on because the doctor ordered it. The social worker sang the same tune as the nurse, but told the boy that he must wear the overcoat and rubbers not only because he was ordered to do so but because it was good for him. This, of course, did not convince the boy that he must wear his overcoat and rubbers, and therefore, we have no way of preventing a chill. Thus, the boy got a rheumatic recurrence.

MISS WHITE: Perhaps it would be more profitable if the social worker, who understands that the prevention of chilling is important, should try to find out why it is that the boy does not care to wear an overcoat and rubbers. This may be the quickest

approach to convincing the boy of the necessity of wearing these clothes.

MISS STROBACK: You spoke a good deal of the need of having a complete picture of the personality of the child. I was wondering how and for what purpose we are to use this complete personality study.

MISS WHITE: Through a study of the personality of the child the caseworker understands his problems and how to establish relationship with him so that she can help him in the various adjustments he must make to his illness and to the restrictions on his activities. She needs the knowledge of the individual's personality to give casework treatment. We have gone a long way in understanding how to use these personality studies. Perhaps some day we are going to find a short cut for the long case history, but I would not look for it at the present time. I believe that the social worker not only must understand the disease, its natural history, its symptomatology, but must also have a keen insight into personality traits and types.

DR. TARAN: You mean, therefore, that the social worker must be a good doctor and an excellent psychiatrist.

MISS WHITE: No, I did not mean that; she must be a good social worker.

#### SUMMARY

DR. TARAN: The rôle of the social worker in the management and control of rheumatic fever was discussed. It was pointed

out that in order to attain the best results, the social worker must play a specific rôle in the general management of the patient suffering from rheumatic fever and rheumatic heart disease. Since the disease is often protracted and frequently leads to severe crippling cardiac disability, careful study and follow-up of the patient and his environment are necessary if the course of the disease is to be influenced favorably. The social worker does not invade the territory of the physician, the nurse or the psychiatrist, but rather deals with those elements in the management of the case which are sociological in nature. The personality of the patient plays an important rôle in the progress of his disease. The relationship of this personality to social environment must be guided by the social worker in such a manner as to create a sensible and practicable adaptation of the patient to his disease, and of his environment to the patient.

It was pointed out that the line of demarcation in the work of the social worker is clear. Trespassing into fields not definitely within the domain of the social worker occurs partly because there is, as yet, little appreciation of the rôle of the social worker in the management of this or other diseases. In most instances, dislocation of the function of the social worker is due to an inadequacy in clinic personnel rather than to confusion as to the field in which the social worker is to operate.

# Conference on Therapy

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## Treatment of Some Chronic Muscular Diseases

**T**HESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students, and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

**DR. HARRY GOLD:** The topic of the conference today is the treatment of some chronic muscular diseases. The opening remarks will be made by Dr. Milhorat.

**DR. ADE T. MILHORAT:** The voluntary muscles comprise about two-fifths of the total weight of the body and are subject to a wide variety of abnormalities of function and structure.

The incidence of the chronic muscular diseases is unknown. Reliable data on this point are lacking. Our experience here at the New York Hospital justifies the opinion that certain of these disorders, namely, progressive muscular dystrophy and progressive muscular atrophy, occur as frequently as many other conditions with which the practicing physician is familiar. Regardless of their actual incidence in the community, I should like to emphasize that to the individual patient the incidence is 100 per cent and is of serious consequence, for many of these disorders are incapacitating and progress ultimately to a fatal outcome.

### MYASTHENIA GRAVIS

This condition is characterized by weakness and fatigability of the muscles. While any of the voluntary muscles may be involved, those earliest and most severely affected are the muscles of the face and throat. Thus, among the most frequent early symptoms are diplopia, ptosis, facial weak-

ness, nasal speech and later, difficulty in swallowing with regurgitation of fluids and an accumulation of saliva in the mouth. In advanced stages, paralysis of the respiratory muscles is a serious complication and may be the immediate cause of death.

Except in the rapidly progressive forms, the course is chronic with fluctuations in the severity of symptoms from time to time. It is often difficult to determine the prognosis in any given case. In many instances, the muscular weakness and fatigability increase over periods of months or years until finally the symptoms are refractory to all types of treatment. On the other hand, some patients improve spontaneously without any known reason and remain relatively or even entirely free from disability for many years. Obviously, the periods of exacerbation and remission of symptoms make it difficult to evaluate the therapeutic measures.

In any therapeutic regimen, the first consideration is rest. The effect of muscular activity induces or increases weakness, and conversely, the beneficial effect of rest on muscular function is often striking.

In many respects, the clinical picture resembles that of curare poisoning in which either neostigmine or physostigmine may promptly abolish the muscular fatigability and weakness. It is, therefore, perhaps not surprising that the drug of choice in the management of myasthenia gravis is neostig-

mine, often referred to under the proprietary name, prostigmine. Neostigmine can be administered orally, subcutaneously or intramuscularly. When given parenterally, the methylsulfate salt is used; the average dose is 0.5 to 1.0 mg. Following subcutaneous or intramuscular administration, definite effects are noted in many patients within a few minutes. Maximal effects are usually noted in about fifteen to twenty minutes and persist for about an hour and a half, after which they gradually subside. Usually the patient's symptoms have returned to their previous status after a period of from two and one-half to three hours following the administration of the drug. Oral administration is the method preferred in the management of ambulatory patients and those in whom disability is moderate. For this purpose, the bromide salt is used, commonly in doses of from 15 to 30 mg., three times daily. In its effect on muscular function an oral dose of 15 mg. is approximately equivalent to a dose of 0.5 mg. given subcutaneously. However, improvement occurs more slowly after oral administration; one-half hour or even longer may elapse before an appreciable effect is noted. Obviously the dosage must be adapted to the needs of the individual patient. As a general rule, the amounts of drug and the intervals between doses should be so adjusted as to provide maximal therapeutic effects without inducing the relatively refractory state that can be induced by excessive doses. It is a common experience that excessive doses of neostigmine usually are followed by exacerbation of muscular weakness and an increased need for the drug. This phenomenon may be explained in part by the pharmacological effect of large amounts of the drug on either the muscle or the motor nerve endplates.

While most patients are able to tolerate relatively large doses of neostigmine, undesirable side effects are occasionally observed.

These include dizziness, pallor, sweating, nausea, vomiting, abdominal cramps and tachycardia followed by a slowing of the heart. They may be prevented or abolished by the oral administration of atropine sulfate in doses of about 0.6 mg. two or three times daily. While the side effects of neostigmine are readily antagonized by atropine, its effects on striated muscle appear to be little, if at all, influenced by this drug.

The effect of neostigmine is commonly considered to be due to its anticholinesterase action, that is, neostigmine inhibits the enzyme that hydrolyzes or destroys acetylcholine. However, experimental evidence indicates that the effect of neostigmine in myasthenia gravis can be due only in part to this mechanism and that neostigmine probably has, in addition, a direct action on the muscle fiber itself.

Physostigmine is less effective than neostigmine. Moreover, undesirable side effects occur more frequently after physostigmine, so that this drug is much less useful than neostigmine in the management of myasthenia gravis.

Patients who are seriously ill with myasthenia gravis often require increasing doses of neostigmine. It appears that the muscles of such critically ill patients become increasingly refractory and require increasing stimulation for their contraction. In such patients the effects of the drug are slower to appear, are less pronounced and persist for shorter periods of time than in patients who are only moderately ill. In some fatally ill patients the subcutaneous administration of 0.5 mg. of neostigmine methylsulfate every twenty minutes may be necessary to prevent complete respiratory paralysis. Recurring respiratory paralysis may require that the patient be placed in a respirator. While in some instances this might conceivably be a lifesaving measure, our experience with the respirator has been disappointing.

A serious complication that requires at-

tention is the accumulation of large amounts of viscid saliva. This may interfere seriously with respiration and should be removed frequently by aspiration.

Severe exacerbations of symptoms are often precipitated by acute infections of the respiratory tract. When the intercurrent infection can be treated satisfactorily with antibiotics, or when the patient can be helped to survive until the infection has subsided, the immediate prognosis may be fairly good. However, if the increase in myasthenic symptoms has been of gradual development and without a precipitating cause that can be successfully treated, the prognosis is grave.

Other drugs that have been used are guanidine and potassium chloride. I have never observed any beneficial effect of guanidine. Only the occasional patient is able to tolerate potassium chloride or obtain any beneficial effect on the muscular symptoms.

The frequent association of a persistent thymus or thymic tumor with myasthenia gravis has long suggested a causal relationship between the two conditions. The incidence of thymic changes in myasthenia gravis is not known and such figures obviously depend on the care with which the thymic area is studied. However, it may be said that in about 50 per cent of our cases and those reported by others there is a hyperplastic tumor or persistence of the thymus. Thymectomy for treatment of myasthenia gravis has been performed in several clinics. While the reports differ with respect to the number of cases, the types of patients and the methods of management, the following conclusions are justified: 10 to 25 per cent of these patients may be considered to have been cured; 20 to 30 per cent were much improved; another 20 to 30 per cent were moderately improved and 7 to 35 per cent showed no improvement. About 15 per cent of the patients died during the

early postoperative period, and 5 to 7 per cent have died since the operation was performed. Because of the high operative mortality, this form of surgical treatment has been discontinued in some clinics. In general, the results seem to be better when the operation is performed relatively early and in patients with only moderate disability.

Irradiation of the thymus is perhaps of benefit in the occasional patient. However, the spontaneous tendency to exacerbation and remission of symptoms makes it difficult to evaluate any type of treatment until a large series is followed for a long time.

#### MYOTONIA CONGENITA (THOMSEN'S DISEASE)

This condition is characterized by an inability to relax the muscles promptly after an initial forceful contraction. Usually it is present from childhood and persists for life. Myotonia has no effect on the normal life expectancy of the patient except when the inability to make bodily movements rapidly may involve the subject in an accident. Since muscular wasting and evidence of other structural changes are absent, the management is limited to measures that diminish or abolish the delay in muscular relaxation. Quinine, given as either the hydrochloride or the sulfate in doses of 0.3 Gm. two or three times daily, often accomplishes this purpose. On the other hand, some patients require as much as 0.6 Gm. of the quinine salt three or even four times daily. When these larger doses are taken, the well known side effects, such as diminution of hearing, tinnitus, visual disturbances and dizziness, frequently limit the usefulness of quinine and many patients consider them more disagreeable than the myotonia. Such patients often limit the use of quinine to special occasions when it is particularly important to be relieved of myotonia. The effect of quinine in myotonia congenita is

probably related to an antagonistic action of the drug on cholinergic stimulation. This opinion is supported by the observation that drugs with cholinergic effects, such as neostigmine, increase the myotonia. Although this effect of neostigmine on myotonia can be prevented or abolished by atropine, atropine is without value in the management of myotonia congenita.

Other drugs affecting myotonia are quinine, the effects of which resemble those of quinine, epinephrine which improves the condition in some patients but is without effect in others and calcium which when given intravenously produces slight but demonstrable diminution in the delay of muscular relaxation. In this clinic, drug therapy is limited to quinine.

#### MYOTONIA ATROPHICA

In contrast to myotonia congenita, in which a disturbance in the function of the muscles is the only clinical feature, myotonia atrophica may present a number of symptoms referable to various organs. In myotonia atrophica, in addition to the myotonia one finds progressive muscular wasting, lens opacities of the type seen in endocrine disturbances, frontal baldness, a low basal metabolic rate sometimes associated with high levels of cholesterol in the blood, and in males, testicular atrophy. The course is insidiously progressive.

At the present time treatment consists only in the management of myotonia with quinine in a manner similar to that in myotonia congenita. Many clinicians prescribe thyroid for the low basal metabolic rate, but this medication is of doubtful value. Various measures, including testosterone and pituitary extracts, have been used but without significant benefit. In general, it may be said that the management of myotonia atrophica is symptomatic and directed mainly toward the control of myotonia. It has little reference to the un-

derlying pathological process and does not significantly alter the progressive course or the ultimate outcome.

#### FAMILIAL PERIODIC PARALYSIS

This syndrome is characterized by periodic attacks of flaccid paralysis. The attacks vary considerably in their extent and severity. Occasionally only one or two of the extremities are affected. In other instances, practically all of the voluntary muscles are involved. Functional disability varies from moderate weakness to complete paralysis with the muscles refractory to all types of stimulation. During particularly severe attacks, respiratory and cardiac involvement may occur. The attacks are associated with low levels of serum potassium. There is no constant level of potassium in the blood at which the attacks occur; usually the decrease amounts to 25 or 30 per cent. The low serum potassium levels are not due to the loss of potassium from the body but to its redistribution in the tissues.

Attacks can be terminated by the oral administration of potassium. We use potassium chloride in a single dose of 5 Gm., repeated in fifteen to thirty minutes if necessary. We prefer the chloride to the bromide salt because of sedative effects of the bromide which are sometimes undesirable. Recovery from paralysis often begins before the level of serum potassium is raised perceptibly, probably due to diffusion of the administered potassium into the muscles. Recurrences can be prevented in many patients by ingestion of from 2 to 4 Gm. of potassium chloride daily. Since the attacks usually have their onset in the early hours of the morning, the potassium sometimes has to be given at about 2 A.M. In other instances, administration before retiring is satisfactory. The ingestion of large amounts of carbohydrate, diuresis induced by copious drinking of water and the administration of epinephrine, ephedrine and insulin may

lower the serum potassium levels and thereby induce attacks of paralysis. These should be avoided as much as possible in the management of periodic paralysis. Some clinicians have expressed the opinion that the administration of thyroid and thiamine chloride are of value, but there is little evidence to support this view.

AMYOTROPHIC LATERAL SCLEROSIS AND  
PROGRESSIVE MUSCULAR ATROPHY  
OF THE TYPE KNOWN AS CHRONIC  
PROGRESSIVE ANTERIOR  
POLIOMYELITIS

No method of management has been demonstrated to have any appreciable influence on the progression of these conditions to a fatal outcome. Various measures have been tried, including the administration of all the known vitamins. One group of workers has claimed favorable results when large amounts of vitamin E were given, but their claims remain unsubstantiated by others. It should be remembered that on the basis of experiments in animals and clinical observations in patients, these syndromes probably result from a variety of causes including infections and deficiencies. Therefore, the basic etiology and hence the therapeutic results in one series of patients might not be duplicated in another series. Clinical improvement has been reported so rarely that satisfactory treatment of patients with these disorders must await increased knowledge. This applies also to muscular wasting of the type known as progressive peroneal muscular atrophy (Charcot-Marie-Tooth disease).

Recently, Mr. Solomon Friedland, a biologist, suggested the use of cytochrome C in a particular case of amyotrophic lateral sclerosis. We had previously tried a long list of other preparations, all of which were without any effect on the symptoms. We have now given cytochrome C intravenously to this and to three other patients in doses

of 50 mg. daily. The effect of this preparation is still being studied in these four subjects, as well as in others with different types of muscular disorders. It is much too early to make a statement on the ultimate value of this material, but so far, the effects are sufficiently striking in this otherwise unresponsive condition as to merit comment. We have noted significant improvement in muscular function, which we are inclined to attribute to relief of the spasm and to an increase in the strength of the partially denervated groups of muscles. The improvement is most evident in the muscles showing only slight wasting, less in those moderately affected and practically or completely absent in the muscle groups in advanced stages of atrophy. In five trial periods in two cases we observed that when the administration of cytochrome C was interrupted, disability increased after a period of from three to five days, but improvement was again apparent in from two to three days after the administration of the material was resumed.

It is of interest that in one patient with severe disability resulting from multiple sclerosis, muscular stiffness and weakness were similarly improved. In one patient with chronic anterior poliomyelitis, improvement in muscular strength was moderate, and in two patients with acute anterior poliomyelitis, decrease in muscle spasm and pain was only suggestive. In two patients with myotonia atrophica, cytochrome C was without effect on the myotonia or muscular weakness.

At the present time, the observations are too incomplete to hypothesize on the mechanism of the action of the cytochrome C in these conditions or to predict the value of this preparation in the management of patients over long periods of time.

PROGRESSIVE MUSCULAR DYSTROPHY

This is characterized by progressive muscular wasting and weakness of the muscles,

often associated with an infiltration and overgrowth of fat (pseudohypertrophy) and a tendency to the development of muscular contractures. While several different forms are recognized, the condition may be considered as a clinical and pathological unit in which the various types cannot be distinguished by any fundamental differences.

The condition resembles in its essentials the muscular dystrophy experimentally induced in animals by dietary deprivation of vitamin E, or by measures that either destroy the vitamin in the intestinal tract or prevent its absorption. For example, the ingestion of large amounts of unsaturated fats may destroy the vitamin, or a biliary fistula with consequent lack of bile may prevent absorption of vitamin E. In the muscular dystrophy of the laboratory, the oral administration of vitamin E is followed by a rapid diminution in creatinuria and a rapid improvement in muscular function and structure. The vitamin is ineffective when given parenterally. In patients with progressive muscular dystrophy, vitamin E is without effect regardless of the mode of administration. This does not necessarily imply that muscular dystrophy in man is not due to a deficiency of vitamin E. In fact, our observations suggest that progressive muscular dystrophy is due to a defect in the utilization of vitamin E, and that the site of this defect is in the gastrointestinal tract. Support for this opinion is furnished by the following observations which we have made during the past few years:

1. If a *normal* subject ingests a test dose of vitamin E, namely, 0.6 Gm. of synthetic alpha tocopherol, and about one-half hour later the gastric contents are aspirated and fed to a patient with dystrophy, there may follow a definite decrease in the creatinuria which appears in twenty-four to forty-eight hours and lasts a few days.

2. In patients with dystrophy, the daily administration of whole wheat germ in

amounts of at least 125 Gm. may likewise decrease the creatinuria, but to a lesser degree than does the vitamin after incubation with normal gastric juice. This effect is reduced but not abolished if wheat germ is given which has been previously extracted with ethyl ether. Wheat germ extracted with ethylene dichloride is without effect, and the residue of the ethylene dichloride extraction contains active constituents which may reduce the creatinuria.

3. Microscopic examination of wheat germ after ethyl ether extraction shows that the pectin portion still contains oily material that is readily removed by ethylene dichloride. Further investigation of all the known constituents of pectin showed that some of the sugars, namely, mannose, galactose or arabinose, were capable of increasing the utilization of vitamin E as indicated by a prompt reduction of excreted creatine and an increase in the output of preformed creatinine when the sugar was administered simultaneously with the vitamin. Inositol and propylene glycol have similar but less marked effects. These findings, therefore, indicate the existence of a group of "accessory substances" which are important in the utilization of vitamin E.

4. Observations in one of our patients suggest that the onset of muscular dystrophy during puberty or even later in life may be influenced by a lack of lactase, the enzyme which is normally present in the intestinal tract and hydrolyzes lactose to equal quantities of galactose and glucose. Although galactose itself was active as an "accessory substance," lactose which normally supplies galactose in this case was without influence on the creatine output. This was the only patient in whom the accessory action of lactose had been studied. On the other hand, raffinose, a trisaccharide that contains galactose and is hydrolyzed by alpha-galactosidase, an enzyme different from lactase, proved active. In fact, galactose given as



raffinose, appeared to have even more effect than galactose itself.

If these sugars and sugar alcohols are necessary for the utilization of vitamin E, the question arises as to whether they are present in the normal gastrointestinal tract. The question is pertinent since vitamin E is effective in animals with experimental muscular dystrophy even if given without food. Gastric mucin promised to be a likely source of accessory substances since its polysaccharide portion is similar to pectin. As we anticipated, we found that in certain patients with dystrophy, gastric mucin is apparently split in the intestinal tract to furnish substances that promote the utilization of vitamin E. We found that when the vitamin was given either with gastric mucin, or with l-fucose, a sugar present in mucin, the creatine output was promptly reduced. Moreover, both galactose and mannose are present in gastric mucin.

The exact nature of the defect responsible for progressive muscular dystrophy in man is not yet established, but the evidence at hand suggests that a lack of these so-called "accessory substances" or a disturbance of the enzyme system involved in their reactions with vitamin E may play an important rôle.

A few patients in whom the downhill course of the disease is relatively slow, have shown clinical improvement when combinations of vitamin E and the "accessory substances" in the form of sugars or mucin are fed to them. On the other hand, no clinical effects have been noted in the majority of patients. It is probable that greater therapeutic effects will result from more efficient preparations of the "accessory substances" or some product of their reaction with vitamin E.

General measures offer little in the treatment of progressive muscular dystrophy. Since prolonged physical inactivity induces more rapid progression of disability and

brings about earlier development of contractures, undue restriction of activity is contraindicated. Physical therapy does not affect the underlying pathological process, but it does help maintain muscular function and prevent contractures and is of real importance in the management of these patients.

Numerous other measures have been employed, including a long list of vitamins and endocrine preparations, which have been without significant effect on the course of the disease.

#### HYPERTHYROIDISM

Occasionally the muscular changes of Graves' disease simulate those of myasthenia gravis, progressive muscular dystrophy or progressive muscular atrophy or increase the disability of these conditions when they are associated. In many of these cases the diagnosis of Graves' disease may be obvious and may suggest the method of treatment, but in others the signs of thyroid dysfunction may be obscure. However, it is known that the muscular changes of Graves' disease are associated with a gross creatinuria which may be abolished by the administration of iodine, whereas the creatinuria of progressive muscular dystrophy appears not to be influenced by the administration of iodine. Furthermore, in muscular dystrophy, although usually not in Graves' disease, the creatinuria is associated with an appreciable reduction in the urinary output of preformed creatinine. These differences are helpful in determining the etiology of the defect in creatine metabolism. Myasthenia gravis is not associated with a significant creatinuria except in those patients whose course is progressing rapidly to a fatal outcome or in those in the advanced stages of chronic disease.

Obviously, when muscular dysfunction is induced or increased by concomitant Graves'

disease, the management must include treatment of the hyperthyroidism.

DR. GOLD: The subject is now open for discussion. Are there any questions?

DR. EPHRAIM SHORR: May I ask, Dr. Milhorat, whether there is any difference in the clinical response to neostigmine in Graves' disease and in myasthenia gravis which might serve as a means of differential diagnosis?

DR. MILHORAT: I think that each of these conditions is likely to respond to neostigmine. The evidence on that point is not clear however, because frequently we do not know whether we are dealing with a myasthenic picture produced by Graves' disease, or with a mild form of myasthenia gravis associated with Graves' disease. I should like to hear what you think about it.

DR. SHORR: In a recent study, Thorn and Eder state that they regard a favorable response to neostigmine as diagnostic of true myasthenia gravis, so that whenever such a favorable response is obtained in a patient with Graves' disease, they infer that the two conditions coexist. However, what Dr. Milhorat says about the failure of neostigmine to differentiate between true myasthenia gravis and a similar clinical picture due to Graves' disease indicates that the differential diagnosis between these two conditions is frequently difficult and sometimes impossible. Problems of this character are met with frequently and indeed, one confronts us on the wards of the hospital at this time. The patient gives a history typical of Graves' disease complicated by a severe exophthalmos. Following a thyroidectomy the patient returned to the hospital with the marked muscular weakness characteristic of myasthenia gravis and an appreciable creatinuria. This patient responds to neostigmine regularly and undoubtedly specifically, as shown by the absence of any effect of placebos. However, in myasthenia gravis we ordinarily expect no creatinuria of any

significant degree except when the condition is profound and generalized and the patient critically ill. We would therefore assume that the creatinuria is due to the thyroid dysfunction and would expect it to be abolished by iodine.

This abolition of the creatinuria of Graves' disease by iodine is generally used to differentiate the myasthenias and myopathies of Graves' disease from true myopathies, such as progressive muscular dystrophy. It is frequently impossible to differentiate these conditions on clinical grounds alone, because the myopathies of Graves' disease simulate very closely those seen in typical progressive muscular dystrophy.

In 1932, studies which I carried out in collaboration with Drs. Richardson and Wolff indicated that the creatinuria of progressive muscular dystrophy is unaffected by iodine. Since then we have had a number of cases of Graves' disease with muscular wasting, sometimes generalized and sometimes confined to the shoulder girdle, and we have relied upon the use of iodine to differentiate these conditions. However, we have since become a little less certain about the universal application of this rule. Seven or eight years ago we studied such a patient in whom severe wasting of the muscles of the shoulder girdle was associated with typical Graves' disease and a marked creatinuria which was completely abolished by the administration of iodine. Following thyroidectomy her Graves' disease subsided and there was a marked improvement in the muscle mass and function. Within the past two years however, this patient, who has remained free of all signs and symptoms of Graves' disease, has developed a progressive spontaneous creatinuria. In this same interval, a brother in his twenties developed typical signs of progressive muscular dystrophy with no evidence whatsoever of Graves' disease.

DR. GOLD: Does she not have both dis-

eases, first Graves' disease and now progressive muscular dystrophy?

DR. SHORR: It is a possibility which must be considered. Her brother, who has typical symptoms of progressive muscular dystrophy, in a recent creatine tolerance test was found to have no spontaneous creatinuria. Apparently then, we may encounter an occasional case of progressive muscular dystrophy in young adults in their twenties, without creatinuria or impairment of creatine tolerance.

DR. MILHORAT: The absence of creatinuria in muscular dystrophy of late onset, for instance in the twenties, is not unusual. While muscular dystrophy is essentially a disease of early childhood, many patients have an onset at puberty. In these cases, muscular wasting is often confined for many years to limited groups of muscles, and creatinuria is either minimal or absent. Ultimately, when the muscular wasting becomes widespread, creatinuria appears and progressively increases. The course in these patients with a negligible degree of creatinuria is usually slow.

DR. SHORR: Certainly the occasional absence of creatinuria in progressive muscular dystrophy reduces the confidence with which we can apply the iodine sensitivity test in the differential diagnosis of this condition. For the most part, however, our own studies, as well as those in the literature, suggest that most instances of such muscle wasting in Graves' disease represent a manifestation of the *one* disease, and may be expected to be corrected by the proper management of the Graves' disease.

DR. MILHORAT: I am not entirely in agreement with Dr. Shorr's point of view. While we all recognize the frequency with which creatinuria and muscular weakness occur in Graves' disease, I believe that all, or nearly all, of the reported instances in which Graves' disease simulates progressive muscular dystrophy, or progressive spinal

muscular atrophy, represent the association of two diseases.

DR. JANET TRAVELL: When a creatinuria is present in myasthenia gravis, is the excretion of creatine influenced by neostigmine? If so, it might help in the differential diagnosis.

DR. MILHORAT: No, neostigmine has no effect on the creatinuria of myasthenia gravis when this is present.

DR. TRAVELL: I should like to ask whether there are any other conditions of disorders of the muscles besides progressive muscular dystrophy and Graves' disease, and perhaps myasthenia gravis, which show a spontaneous creatinuria?

DR. MILHORAT: Spontaneous creatinuria may occur in any process that results in wasting of most of the muscles of the body. An outstanding example of this is dermatomyositis. In that condition the muscular wasting can be as extensive as that seen in the advanced stages of muscular dystrophy, and the creatinuria is likewise of the same order as in muscular dystrophy.

DR. TRAVELL: With impaired retention of ingested creatine?

DR. MILHORAT: Yes. The impairment in retention of creatine may be so gross that all of an ingested test dose will be excreted in the urine.

DR. TRAVELL: Do these cases respond to vitamin E?

DR. MILHORAT: They do not respond to vitamin E given alone.

DR. TRAVELL: What are the normal values for the twenty-four-hour excretion of creatine in the urine and for the retention of ingested creatine?

DR. MILHORAT: The normal adult male excretes either no creatine at all or only negligible amounts, that is, up to 42 mg., and is able to retain all or practically all of an oral test dose of from 1 to 2 Gm. of creatine. Women often excrete up to 60 mg. of creatine daily and the retention of in-

gested creatine is somewhat lower than in men; a retention of 75 per cent or more of the test dose is usually considered normal. Infants and children normally excrete appreciable amounts of creatine depending on their age, and they retain less ingested creatine than adults.

DR. GOLD: Dr. Shorr, do your values for the normal agree with these figures?

DR. SHORR: Yes. We take about 50 mg. of creatine in twenty-four hours as the upper limit of the normal excretion on a creatine-free diet, but minor increases above this amount are not considered significant. Men usually excrete slightly less than 50 mg. We find that normal individuals when given a test dose of 1.32 Gm. of creatine, usually retain at least 70 per cent of the dose; men on the average, retain somewhat more than women.

DR. TRAVELL: How does the ingestion of protein influence the urinary excretion of creatine?

DR. MILHORAT: Large amounts of protein may increase the excretion of creatine, since the substances from which the body builds creatine are the amino acids, glycine and arginine. The methyl group of creatine can be furnished either by the amino acid methionine or by choline.

DR. TRAVELL: In studying creatine metabolism, it is important then, to put the subject on a "creatine-free" diet, which contains no meat or fish products, during the period of urine collection

DR. MILHORAT: Yes. About 95 per cent of the creatine in the body is found in the muscles, and since meat and fish products are usually derived from muscle tissue, diets not free from these foodstuffs will contain large and undetermined amounts of creatine. When meat or fish are eaten, one cannot tell how much of the excreted creatine is lost from the patient's muscles and how much is derived from food.

DR. TRAVELL: From how much protein is

1.32 Gm. of creatine derived? That is the amount used in the standard creatine tolerance test.

DR. MILHORAT: Ox muscle contains about 400 mg. of creatine per 100 Gm. of muscle. Therefore, 1.32 Gm. of creatine represents about three-quarters of a pound of meat. Vegetable protein does not contain creatine but is rich in the materials from which creatine is made in the body.

DR. TRAVELL: You spoke of changes in the output of creatinine as being of diagnostic significance in progressive muscular dystrophy. Would you tell us what are the normal values for the excretion of this material and its relation to the creatine output?

DR. MILHORAT: The muscles convert creatine into creatinine which is then promptly excreted in the urine. The amount of creatinine in the urine has a definite relationship to the total mass of the body. Thus, men with large, well developed muscles, as a rule, excrete more creatinine than do women, and adults, more than children. The normal man excretes about 25 mg. of creatinine per Kg. of body weight per day and the normal woman about 15 to 20 mg. This amount is reduced in muscular dystrophy in proportion to the degree of muscular wasting and may be as low as 3 to 5 mg.

DR. TRAVELL: We have a group of patients, both men and women, who show a spontaneous creatinuria and impaired retention of creatine and who do not exactly fit into any of the categories described by Dr. Milhorat. These are physically active persons without visible muscular wasting and whose major complaint is a chronic pain apparently of a muscular origin. They have recurrent attacks of severe and at times incapacitating pain which is associated with spasm and tenderness of the muscles. As a rule, physical examination is otherwise negative, and all sorts of laboratory tests except the creatine tolerance test are also

normal. Dr. Shorr has been interested in these patients. The usual diagnosis in such cases has been chronic fibromyositis, although we prefer the term chronic myalgia or fibromyalgia, which is clinically more descriptive since evidences of infection are usually lacking. Brochner-Mortensen in 1941 reported in the *Acta medica Scandinavica* that he found a significant creatinuria in a similar group of twenty men with myalgia, or myosis, as he called it. I should like to ask Dr. Milhorat whether he has observed any such cases?

DR. MILHORAT: I have seen similar patients with these muscular symptoms and creatinuria.

DR. TRAVELL: Does the creatinuria in these cases respond to vitamin E when given together with the factors which increase its utilization?

DR. MILHORAT: No, we have not detected any such response.

DR. TRAVELL: Then, would you say that this type of disorder is not related to dermatomyositis?

DR. MILHORAT: The condition appears to be different from dermatomyositis in many respects.

DR. TRAVELL: In view of your finding that certain "accessory factors" are necessary for the utilization of vitamin E in progressive muscular dystrophy and dermatomyositis, as indicated by changes in the urinary excretion of creatine, would you say that these conditions represent nutritional deficiencies?

DR. MILHORAT: In my opinion, progressive muscular dystrophy probably has such an etiology. It is not due to a dietary deficiency but rather to a utilization defect possibly something like that seen in pernicious anemia. We do not have enough data on which to make a statement for the remainder of these muscular diseases.

DR. MAYNARD B. CHENOWETH: Dr. Milhorat, can you give us any information

about di-isopropyl-fluorophosphate in the treatment of myasthenia gravis?

DR. MILHORAT: Such limited observations as I have made suggest that this agent offers no advantage over neostigmine and probably will not find a prominent place in the management of myasthenia gravis.

DR. McKEEN CATTELL: Dr. Riker has made some observations which bear on Dr. Chenoweth's question.

DR. WALTER RIKER: The rationale for the use of di-isopropyl-fluorophosphate, or DFP for short, in this condition was based on the fact that this agent is a potent inactivator of cholinesterase. In contrast to neostigmine or physostigmine, DFP effects an irreversible inactivation of cholinesterase, as demonstrated by Mazur and Bodansky. Dr. Clarke Wescoc and I administered DFP to patients suffering from myasthenia gravis. The doses employed were increased gradually in order to decrease the cholinesterase activity of red blood cells to levels approximating 20 to 30 per cent of normal. These patients did not manifest any definite improvement in response to DFP therapy. We were of the opinion that the response to neostigmine was somewhat better after the DFP, but we were unable to evaluate this with any degree of certainty.

We were struck by the fact that doses of neostigmine, of the order of 0.5 to 1.0 mg. given parenterally, had virtually no effect on red blood cell cholinesterase, and yet produced the characteristic amelioration of symptoms. We investigated the actions of DFP and neostigmine in the experimental animal. We found that the intra-arterial injection of DFP alone produced a series of fasciculations after a latency of one to five minutes. Neostigmine alone, injected arterially, produced an immediate contraction of the muscle followed by a series of weaker and repetitive contractile responses. This also occurred when neostigmine was similarly injected after the intra-arterial injection

of DFP and at a time when the cholinesterase of the muscle was found to be completely inactivated. This action of neostigmine in the absence of cholinesterase was further substantiated in chronically denervated muscle in which an immediate acetylcholine-like contracture was produced by the intra-arterial injection of this agent. In contrast to this, DFP was entirely without effect. We concluded that neostigmine, among other actions, exerts a direct action on striated muscle, and that its therapeutic value in myasthenia gravis is due to this direct action which is similar to that of acetylcholine.

DR. CHENOWETH: Would you and Dr. Milhorat agree that the efficacy of neostigmine in myasthenia gravis is due to its direct action on the muscle?

DR. MILHORAT: No, I would not. It is possible that all the therapeutic effects of neostigmine and physostigmine are due to a direct action on the muscle, but the clinical evidence is not sufficient to warrant such a statement.

DR. GOLD: Dr. Milhorat, you said that if a patient with myasthenia gravis continues to receive neostigmine there is a tendency for the development of tolerance so that the patient requires increasing amounts of the drug to secure the same effect, and that if the doses are excessive, aside from toxic symptoms relating to other structures, the muscular weakness may actually increase. Why does the muscular weakness increase? How do you view the development of tolerance?

DR. MILHORAT: I think that the increasing need of the patient does not represent the development of true tolerance but rather the development of a relatively refractory state of the muscle. It is probably due to the fact that the patient is worse than he was before. I am speaking now of changes over a long period of time.

DR. GOLD: Do you mean that the disease has progressed or that a need for larger doses

of the drug has developed because of its prolonged use?

DR. MILHORAT: The disease has progressed, and therefore greater stimulus is required for muscular contraction.

DR. GOLD: Now for the other question, what is the mechanism by which excessive doses of neostigmine make the muscular condition worse?

DR. MILHORAT: As I have said, when very large doses of neostigmine are given, within a matter of a few hours or a day there follows a period during which increased doses of the drug must be given. It can be demonstrated at this time that doses of neostigmine which previously had induced a favorable change, will now produce a far smaller change. Why that is, I do not know.

DR. GOLD: That does not quite explain why large doses make the patient worse.

DR. RIKER: It is well known that an excessive accumulation of acetylcholine at the neuromuscular junction results in a refractory state of the muscle. In the experimental animal, when the cholinesterase in the muscle is inactivated by di-isopropyl fluorophosphate, the subsequent injection of acetylcholine leads to a refractory state of the muscle so that it is unresponsive to both acetylcholine and nerve stimulation. A similar effect is observed when neostigmine is used instead of acetylcholine. As Dr. Milhorat has mentioned, excessive doses of neostigmine to patients with myasthenia gravis usually result in an increased degree of muscular weakness. In this and other respects, neostigmine behaves like acetylcholine. I think it should be stressed that in the management of myasthenia gravis, the dose of neostigmine should be strictly limited. Certainly it is the only really effective agent available. Since large doses may be harmful, the aim in treatment should not be to restore complete function, but only to effect some improvement and

thus avoid the risk of producing a refractory state in the muscle.

DR. GOLD: I wonder if we could have a word on the possible use of DFP in myotonia congenita?

DR. CATTELL: It might sensitize to the curare-like action of acetylcholine in the muscle, but since DFP reduces cholinesterase this latter action might make the myotonia worse because of the resulting increase in acetylcholine.

DR. GOLD: I was wondering about producing the curare-like action of DFP while blocking the cholinergic action of DFP by means of atropine.

DR. CATTELL: DFP does not have a direct curare-like action. The curare-like effect appears only because DFP allows the accumulation of acetylcholine.

DR. GOLD: I was referring to the observations in cats, namely, that large doses of DFP produce cholinergic effects which can be counteracted by atropine, and also muscular weakness and fatigue that is not overcome by atropine. I believe that the latter action sometimes lasted for months after the dose and in some cases seemed permanent. These animals sometimes behaved like patients with myasthenia gravis. Such an action might possibly be of value in myotonia congenita.

DR. CHENOWETH: In regard to the action of curare in myotonia congenita, there is an experimental condition resembling myotonia in which a drug, namely, 2,4 dichlorophenoxy acetic acid, or 2,4 D for short, produces in rabbits an inability of the muscles to relax; it is associated with fine fasciculation of the muscle fibers. The analogy extends further, in that the symptoms can be completely abolished by quinine and partially relieved by calcium. However, curare in any dose, given as intocostin, does not influence the condition.

DR. MILHORAT: The answer is that these have never been tried.

DR. CATTELL: In line with that, curare is now being used clinically in various muscular disorders. Has that been tested in any of the diseases which you have mentioned?

DR. MILHORAT: It has been tried in various spastic states of a muscle, but I know of no instance in which curare has been used for the treatment of myotonia.

DR. CATTELL: It would be desirable to know the answer. Most of us assume that the effect of quinine is related to its curare-like action.

DR. SEYMOUR H. RINZLER: Would Dr. Milhorat explain the efficacy of neostigmine in such widely different conditions as myasthenia gravis, in which there is flaccidity of the muscles, and those disorders which are characterized by spasticity of the muscles, for instance the spastic paralysis following cerebral thrombosis or acute anterior poliomyelitis. There are numerous reports of the successful use of neostigmine in such spastic states.

DR. MILHORAT: I know that much has been said about its usefulness in patients with spastic conditions, but I have never seen any beneficial effect of neostigmine in decreasing spastic states of muscles. In fact, certain types of muscular rigidity, for example that of Parkinson's disease, are increased by neostigmine.

DR. GOLD: Dr. Milhorat, would you say something about aminoacetic acid, or glycine? We used to hear a lot about that in the treatment of muscular dystrophy.

DR. MILHORAT: Aminoacetic acid was employed for some time, but it is no longer used to any great extent in the management of patients with progressive muscular dystrophy or myasthenia gravis. It appears to be of some value in myasthenia gravis, but the effect of glycine is so small when compared to that of neostigmine, that we find it unprofitable to use. In progressive muscular dystrophy, glycine is without effect in

most instances. However, in those forms in which the symptoms appear late, namely, in the Landouzy-Dejerine type, amino-acetic acid is sometimes of value in decreasing muscular fatigue, although it apparently has no effect on the underlying dystrophic process.

DR. WALTER MODELL: Years ago ephedrine and amytal were popular in the treatment of myasthenia gravis. What has happened to them?

DR. MILHORAT: Ephedrine sulphate given in doses of about 7 mg. three times a day by mouth, frequently is of value in myasthenia gravis, but so many patients complain of the side effects, such as headache and tachycardia, that the usefulness of that drug is limited. Patients who require increasing doses of prostigmine usually are given at least a trial of ephedrine, and in certain instances it is a valuable adjunct.

DR. MODELL: You use it without amytal? Once it was combined or mixed with it.

DR. MILHORAT: In my experience, amytal is contraindicated. Many patients with myasthenia gravis complain of increased weakness following the use of sedatives.

DR. GOLD: There is a nice pharmacological observation in your application of neostigmine. You stated that the peak effect after intramuscular injection is reached within less than half an hour, after which the effects begin to wear off and in about three hours have largely disappeared. The patient with myasthenia gravis provides us with the curve of action of neostigmine, because there are fairly sharp end-points to mark the beginning and end of the effect. Neostigmine is often used for intestinal distention in a dose given once every six hours or so. It is clear from Dr. Milhorat's observations that, if the first dose does not accomplish the result, the second dose repeated six hours later will not do anything either, because under those conditions, there is no cumulation of the drug. This

has nothing to do directly with muscle diseases, but here there is the opportunity to make an important type of pharmacological observation. Are there any more questions?

DR. MILHORAT: May I just make one historical comment?

DR. GOLD: Please do.

DR. MILHORAT: Sometimes we think that our concepts of physostigmine actions are of recent origin. In his article published in the *Klinische Wochenschrift*, January 7, 1895, Jolly described the myasthenic reaction with which his name is often associated. While the response of the muscles in myasthenia gravis appeared to be normal when faradic current was employed, definite fatigability was demonstrated with the use of a tetanizing current. After each succeeding stimulus, the response became less complete until finally the contractions ceased entirely. Jolly also pointed out that certain alkaloids, namely veratrine and physostigmine, may induce changes in the muscle that resemble those seen in myotonia congenita. Since the muscular state in myasthenia gravis appeared to be the opposite of that seen in myotonia congenita, Jolly suggested that pharmacological agents such as physostigmine, which induce a pharmacological effect opposite to that of the myasthenic reaction, should be sought for in the management of myasthenia gravis. Physostigmine was tried by Jolly, but the side-effects were so pronounced that he thought the use of the drug would have to be restricted to patients under observation in a hospital.

#### SUMMARY

DR. TRAVELL: The list of chronic diseases of the skeletal muscles which we have considered today includes myasthenia gravis, myotonia congenita, myotonia atrophica, familial periodic paralysis, amyotrophic lateral sclerosis, progressive muscular atro-



phy, progressive muscular dystrophy, the myopathies of Graves' disease, dermatomyositis and fibromyositis (fibromyalgia).

These conditions are distinguished from each other by a variety of clinical features and their differential diagnosis is not ordinarily difficult. However myasthenic symptoms may sometimes complicate the picture of Graves' disease and raise the question of the coexistence of a primary muscular dystrophy and hyperthyroidism. The fact that iodine administration in Graves' disease reduces the spontaneous creatinuria and increases the retention of creatine often serves to differentiate the two. Neostigmine relieves the myasthenic symptoms in both conditions and does not influence creatine excretion in either. In view of the diagnostic, and at times prognostic value of the creatine tolerance test, the normal values and standard conditions for this test are discussed.

The causes of the chronic muscular diseases listed above are unknown and their treatment is, for the most part, unsatisfactory. The drugs and measures which received special consideration are neostigmine, thymectomy, quinine, ephedrine, epinephrine, calcium, potassium chloride, cytochrome C, vitamin E with accessory factors and glycine.

In myasthenia gravis, removal of the thymus appears to cure a small proportion of cases. Neostigmine is highly effective in relieving the muscular weakness and fatigue. It is a double-edged sword and proper dosage is a matter of the greatest importance. There was a belief that the therapeutic effect resulted from its inhibition of cholinesterase, but now there is new evidence indicating that the beneficial effect is due to direct stimulation of the muscle, and

that excessive doses may increase the weakness through the anticholinesterase action which gives rise to a curare-like effect of the increased acetylcholine at the muscle.

In familial periodic paralysis, an oral dose of 5 Gm. of potassium chloride often relieves the attack promptly, and doses of 2 to 4 Gm. daily may prevent recurrences.

In myotonia congenita, quinine, in oral doses of from 0.3 to 0.6 Gm. several times daily, often accelerates the muscular relaxation after a movement. Epinephrine and calcium are also sometimes of value.

There are preliminary observations indicating that daily intravenous doses of 50 mg. of cytochrome C may control the muscular disability of amyotrophic lateral sclerosis and related diseases.

New observations suggest that in progressive muscular dystrophy and dermatomyositis certain "accessory substances" are needed for the utilization of vitamin E, as indicated by diminished urinary excretion of creatine, following their administration. Preparations which when fed together with vitamin E to patients with these disorders have been shown to have an effect on creatine excretion, include normal gastric juice, certain sugars present in pectin and wheat germ, and also gastric mucin which contains some of the polysaccharides shown to act as "accessory substances." The clinical importance of these dietary factors has not as yet been satisfactorily demonstrated. The results open up the vista, however, that the etiology of these, and possibly of other members of this group of diseases, may be specific nutritional defects, and point the way to new lines of investigation for the solution of the vexing problems of therapy in these progressive muscular diseases.

# Clinico-pathological Conference

## Hemiplegia Due to Intracranial Mass<sup>\*</sup>

**S**TENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

**T**HE patient was a sixty year old white, retired railroad employee who entered the Barnes Hospital on April 23, 1946, complaining of paralysis of the left arm and left leg. The family history was of interest in that the patient's mother had died of diabetes at the age of sixty-nine. The patient had enjoyed excellent health for most of his life. In childhood he had had several bouts of an illness described as malaria. At the age of forty-two he injured his leg and an infection developed which subsequently involved the bone. Following an operation there was complete recovery. The patient had been told that he had a large perforation of the nasal septum; he had never had an operation or injury involving the nose and was unaware of the origin of the perforation. Two years before admission he developed a hacking cough which was productive of thick, white sputum but never of blood. X-rays of his chest taken shortly after the onset of the cough were said to have shown "healed scars." One year prior to entry the patient stopped work because of increasing fatigue and eight months before admission he developed shortness of breath on exertion. For years he had consumed six drinks of whisky daily. In the year before entry he had lost no weight.

Nine days before admission, while walking, the patient noticed that his left foot seemed to swing out with each step; concomitantly his left arm felt "half asleep."

Within a few minutes these complaints cleared completely and the patient was symptom-free until twenty-four hours later when he began to have jerking movements of the left leg and a sensation of tightness in the muscles of the left leg and arm. After several minutes the jerking movements stopped but from then on the patient was aware of a marked limitation in the use of both the left arm and leg. However, he was still able to walk without assistance. He was seen by a physician who told him that his blood pressure was "90." The patient was not dizzy, disoriented or weak. He slept well that night but on the following morning had paresthesias of the left arm and leg. Subsequently, the left arm and leg became progressively weaker and finally totally paralyzed. Aside from an occasional slight frontal headache the patient had had no other symptoms.

At the time of entry physical examination revealed the temperature to be 37°C., pulse 70, respirations 26 and blood pressure 130/80. The patient was a well nourished and well developed male who appeared comfortable and not ill. His complexion was florid. He coughed frequently during the examination and during the periods of coughing he became cyanotic. Aside from an ecchymosis over the left iliac crest the skin appeared normal. The pupils were equal and reacted well to light and accommodation. Examination of the fundi re-

<sup>\*</sup> From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

vealed the discs and vessels to be normal; no hemorrhages or exudates were seen. The nasal septum was deviated to the right; a perforation, 1 cm. in diameter, was noted. The teeth were absent. The pharynx was moderately injected. The trachea was in the midline. On percussion the chest was hyperresonant throughout; the breath sounds were somewhat distant. Scattered moist râles and a few rhonchi were heard at the right base and in the right axilla. The heart was not enlarged and the sounds were rather distant; the second aortic sound was louder than the second pulmonic sound. The rhythm was regular and there were no murmurs. Examination of the abdomen revealed it to be soft; no organs or masses were palpable. The prostate was small. A well healed scar was noted over the left tibia. Neurologic examination revealed generalized constriction of the visual fields and slight ptosis of the left eyelid. There was no speech abnormality. The tongue deviated slightly to the right. The muscles on the left side of the neck were weak; the left trapezius was atrophied as was the left deltoid group. There was complete paralysis of the left arm and leg. No fibrillary twitchings were seen. Sensory examination was entirely normal. The left biceps and knee jerk were hyperactive; the toe signs were not pathologic.

The laboratory studies were as follows: Blood count: red cells, 4,640,000; hemoglobin, 14 Gm.; white cells, 6,400; differential count: stab forms, 10 per cent; segmented forms, 60 per cent; lymphocytes, 24 per cent; monocytes, 6 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total protein, 5.9 Gm. per cent; albumin, 3.5 Gm. per cent; globulin, 2.4 Gm. per cent; sugar, 73 mg. per cent; cephalin-cholesterol flocculation test, negative. Icterus index: 3. Sputum examination: no acid-fast bacilli found. Prothrombin time: 75 per cent of normal.

Bleeding time: three minutes, ten seconds. Clotting time: eight minutes, sixteen seconds. Lumbar puncture: initial pressure, 190 mm. of water; final pressure, 160 mm. of water; cells, 6 lymphocytes; protein, 134 mg. per cent; sugar, 67 mg. per cent; chlorides, 124 milli-equivalents/liter; colloidal gold curve, 2222221000; Wassermann, negative. Roentgenogram of the chest: "The heart is slightly enlarged. The hilar shadows are large and contain many round deposits of calcification. There are several emphysematous blebs in the apex of the right upper lobe. There is moderate scoliosis of the thoracic spine with convexity to the left." Stereoscopic views of the skull: indeterminate. Electrocardiogram: normal.

Shortly after admission several observers detected the liver edge at the right costal margin and the tip of the spleen was likewise felt. On three occasions the urine was positive for bile. Liver function tests were as follows: icterus index, 9; alkaline phosphatase, 11 Bodansky units; bromsulfalein test, 22 per cent retention in 30 minutes. Several days after admission new ecchymotic areas appeared on the paralyzed side. A Rumpel-Leede test was positive. The platelet count was 234,000. Five days after entry a second lumbar puncture was performed. On this occasion the initial pressure was 90 and the final pressure 70 mm. of water. There were 9 lymphocytes; the protein was 139 mg. per cent, the chlorides 124 milli-equivalents/liter, the colloidal gold curve 1111110000, and the Ayala index 6.6. An electroencephalogram revealed a focus of borderline slow activity in the right temporo-occipital region.

On repeated examination wheezes were heard over both lungs and other signs consistent with emphysema were recorded.

On the eleventh hospital day the patient had a clonic convulsion which began in the left arm and which was accompanied by mild twitching of the left thigh muscles.

The episode lasted twenty-five minutes but there was no spread. Subsequently, several similar but more severe attacks occurred. Shortly after the first one began the patient had a shaking chill and his temperature rose to 39.7°C. Physical examination at this time revealed only injection of the conjunctivae and many moist râles in the right axilla and at the right base. The white blood count was 11,250 with 15 per cent stab forms, 73 per cent segmented forms and 12 per cent lymphocytes. Another roentgenogram of the chest showed little change from the findings on the first film. A blood culture was sterile. The urine examination remained normal except for occasional traces of bile. The purpura persisted but no further blood abnormalities were detected. Two weeks after admission the patient complained of abdominal pain and was noted to have tenderness and moderate muscle spasm in the epigastrium. His temperature continued to spike to 39°C. frequently and his white cell count rose to 14,000. Oral cholecystography was done and the gall-bladder was not visualized. An x-ray diagnosis of a "pathologic" gallbladder was made. A flat film of the abdomen revealed no abnormalities except for hypertrophic osteoarthropathy of the lumbar spine. After three and one-half weeks on the neuromedical service the patient was transferred to the neurosurgical service where the following positive findings were recorded on examination. There was a complete left facial paralysis and definite weakness and atrophy of the left sternomastoid and trapezius muscles. The left arm and hand were completely paralyzed and there was atrophy of the deltoid, triceps, and biceps groups as well as of the thenar muscles of the left hand. The left triceps and biceps reflexes were hyperactive. The intercostal muscles on the left seemed weak and the abdominal reflexes were absent bilaterally. The left leg was entirely paralyzed and vibratory sensation

was absent. The knee jerk was hyperactive and the Babinski sign questionably positive. The sensory examination again was normal. Ventriculograms were done and the x-ray films showed a shift of the pineal gland to the left. There appeared to be a circular defect compressing the posterior part of the body of the right ventricle. Following ventriculography the patient was taken to the operating room; on exploration a necrotic area was encountered at a depth of 3 cm. in the right parietal area. Adjacent to the area of necrosis there was a firm, well demarcated tumor about the size of a plum; this mass was excised. Postoperatively the patient did poorly and failed to regain motion in the left upper or lower extremities. He continued to have fever as high as 40.4°C. and his blood pressure fell to 98/68. He was placed in an oxygen tent and given whole blood transfusions and penicillin. A ventricular tap was performed but no evidence of increased intracranial pressure was found. Considerable respiratory difficulty required almost constant use of a suction apparatus. The patient responded enough to talk slightly but his respiratory difficulty persisted and shortly before death, Cheyne-Stokes breathing was noted. He failed rapidly and despite all supportive measures he died on May 26, 1946.

#### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient's illness was rather complicated. He had a chronic cough for several years, a palpable liver and spleen, x-ray evidence of a pathological condition of the gallbladder, signs suggesting mild liver insufficiency, and finally, neurologic signs suggestive of a brain tumor. Dr. Levy, from the data available, may the diagnosis of brain tumor be substantiated?

DR. IRWIN LEVY: That diagnosis was not obvious at the onset but there were clues which led one to suspect that a subcortical

brain tumor was present. Three factors in particular stand out; one, the progressive nature of the clinical symptomatology—particularly of the hemiparesis; two, the occurrence of convulsive seizures which are much more common with subcortical tumors than with vascular lesions; and three, the high spinal fluid protein on two different occasions.

DR. ALEXANDER: Do the ventriculograms confirm the diagnosis?

DR. LEVY: Yes, they definitely indicate a space-taking lesion.

DR. ALEXANDER: Apparently at the time of operation this tumor was well demarcated and easily excised. From this fact would you comment on the probable nature of the lesion?

DR. LEVY: Most subcortical tumors that can be shelled out without difficulty represent metastatic lesions.

DR. ALEXANDER: May the fever which was recorded during this patient's illness be explained on the basis of the brain lesion and particularly by the presence of areas of necrosis?

DR. LEVY: Acutely developing primary tumors may in themselves cause temperature elevation.

DR. ALEXANDER: This patient had a rather high degree of fever; frequent elevations to 39°C. were recorded.

DR. LEVY: Usually the fever associated with brain tumor is of a lesser magnitude.

DR. CARL G. HARFORD: In what portions of the brain is involvement by tumors most apt to produce fever?

DR. LEVY: One cannot be specific in answering that question. Various centers are recognized which are related to the vasomotor system. For example, area 6, the orbital surface of the frontal lobe, and certain areas in the hippocampus are thought to have autonomic function transmitting impulses to the hypothalamus and to the brain stem thus influencing body tempera-

ture. The hypothalamic centers which lie on either side of the optic chiasm may, when involved, give rise to hyperthermia or hypothermia. I have seen instances, when the posterior portion of the hypothalamus was involved, in which temperatures as low as 96°F. were persistently noted. As mentioned before, however, acutely developing tumors, regardless of their localization, are frequently associated with some temperature elevation.

DR. ALEXANDER: Would the amount of necrosis present in the tumor be related to the febrile response?

DR. LEVY: I do not think so for there is not good absorption from the brain.

DR. ALBERT ROOS: Dr. Levy, you stated that the lesion probably was located in the subcortical area. Does not the occurrence of convulsions suggest involvement of the cortex itself?

DR. LEVY: When the patient's presenting symptom is generalized convulsion, statistically a subcortical lesion is favored. When the cortex is involved, a Jacksonian march is more apt to occur.

DR. ALEXANDER: Dr. Levy has suggested that the tumor in the right parietal area was metastatic. If we consider this lesion to have been metastatic, where did the primary tumor arise? Frequently metastatic tumor of the brain is secondary to carcinoma of the lung. Dr. Goldman, do you believe the pulmonary signs and symptoms indicate that this patient had a lung tumor?

DR. ALFRED GOLDMAN: The prominent pulmonary symptoms in the history were cough, non-bloody sputum and dyspnea. Such symptoms plus the signs elicited in the physical examination suggest emphysema and bronchitis rather than a primary tumor. The x-ray findings were consistent with pneumonitis. However, as you have pointed out, Dr. Alexander, frequently metastatic tumors in the brain arise in the lung and bronchogenic carcinomas often are not

visible on x-ray. Sometimes the primary lesion is very small and if there is no bronchial obstruction, one is unable to identify the primary site.

DR. ALEXANDER: It is very important for us to determine, if this be a metastatic lesion, the primary site, and to discuss the mechanism by which the metastasis occurred. If the primary tumor was not in the lung, but rather in some other viscus, I would like to ask Dr. Robert Moore what the evidence is that tumor cells may pass through the lungs without giving rise to metastases there.

DR. ROBERT A. MOORE: Such a phenomenon has been postulated because of the fact that the pulmonary capillaries are slightly larger than the systemic capillaries. It has been suggested that individual tumor cells may pass through the lung to other sites. The recent evidence set forth by Batson regarding the vertebral veins as a pathway of metastases seems a much more logical explanation and has cast doubt on the previous hypothesis.

DR. ALEXANDER: This patient also had signs suggesting liver disease. Bile was found in the urine on several occasions. Would you discuss the liver function studies, Dr. Moore?

DR. CARL V. MOORE: This patient had a normal icteric index, a negative cephalin-cholesterol flocculation test, but an elevated alkaline phosphatase and definite bromsulphalein retention. These data suggest that there may have been localized lesions in the liver which may have accounted for the occasional presence of bile in the urine.

DR. ALEXANDER: Dr. Wade, do you believe the focal lesions were metastatic?

DR. LEO J. WADE: I believe this patient had obstructive jaundice but I am not sure that the obstruction was due to carcinoma. It is possible that there was a common duct stone which produced intermittent, low-grade obstruction.

DR. W. BARRY WOOD, JR.: Would not



FIG. 1. Carcinoma of the esophagus; photograph of gross specimen.

the abdominal pains likewise suggest intermittent obstruction?

DR. ALEXANDER: There is considerable evidence to suggest gallbladder disease. The fever might have been due to common duct obstruction; if present, obstruction due to a stone bore no relation to the central nervous system lesion. Dr. Wade, may a focal lesion in the liver produce intermittent obstruction?

DR. WADE: I rather doubt that this occurs very often. Usually obstruction is not seen in metastatic disease unless there is invasion of the biliary tree and under such circumstances obstruction is usually complete.

DR. ALEXANDER: If you are considering the possibility of a tumor, would the fact that this patient had a definite alcoholic history influence your reasoning?

DR. WADE: I would be more concerned with his dietary history than with his alcoholic history. If the patient had adequate dietary habits, I do not believe that the amount of alcohol he consumed would have been significant.

DR. ALEXANDER: Dr. Reinhard, would you discuss the purpura which was noted in this case?

DR. EDWARD H. REINHARD: The data available do not indicate any abnormality in the clotting mechanism and one would therefore have to assume that the defect present involved the capillaries. I have no good explanation for possible increased

capillary permeability in this case. It is occasionally seen in carcinomatosis, but carcinomatosis seems unlikely here.

DR. ALEXANDER: It is of interest that the purpura was confined to the paralyzed side. Dr. Levy, have you seen this phenomenon before?

DR. LEVY: One notes vasomotor changes on the involved side in hemiparesis but I have not seen purpura before.

DR. WOOD: Is not edema the usual unilateral clinical manifestation in hemiplegia, Dr. Levy?

DR. LEVY: Yes.

DR. ALEXANDER: Are there any further suggestions?

DR. WOOD: It does not seem certain to me that this patient had a carcinoma. He gave no history of weight loss in the year preceding entrance to the hospital, and no evidence, either clinical or roentgenologic, was ever obtained of a tumor other than in the brain. The calcified hilar lymph nodes were prominent and suggest the possibility of either tuberculosis or histoplasmosis. I believe tuberculoma of the brain should be considered and I would like to know Dr. Goldman's opinion regarding the possibility of tuberculosis.

DR. GOLDMAN: Although I thought of tuberculoma as a possible explanation of the central nervous system lesion, the description at operation does not seem compatible. The appearance of the calcification in the hilar lymph nodes suggests the so-called "egg shell calcification" which is associated frequently with silico-tuberculosis.

DR. WOOD: Are lesions in the brain common in histoplasmosis?

DR. ROBERT J. GLASER: In the seventy-one cases described in the extensive review of Parsons and Zarafonetis,\* involvement of the brain is recorded only once.

DR. WADE: There is a suggestion of su-

perior vena cava obstruction, possibly from a mediastinal mass, for the patient is described as having had florid complexion and is said to have become cyanotic when he coughed.

DR. ALEXANDER: As has been pointed out, however, this man had many signs suggesting emphysema and in such a patient those changes may be observed.

DR. HARFORD: There appeared to be slight elevation of the right leaf of the diaphragm. Could this be considered evidence of a metastatic lesion in the liver?

DR. DONALD S. BOTTOM: The diaphragm on the right had a lobulated appearance which is seen not infrequently in normal patients; however, without a lateral view, it is not possible to rule out completely either a supradiaphragmatic or subdiaphragmatic lesion.

DR. ALEXANDER: In view of the emphysema would you not have expected the diaphragms to be lower?

DR. BOTTOM: Usually they are low in emphysema.

DR. ALEXANDER: In summary, it seems that the consensus of opinion of the staff favors a metastatic rather than a primary lesion in the brain. If the lesion be metastatic, the site of origin is not at all clear. The lungs seem to be an unlikely primary site and the evidence does not point to any other specific region. It is believed that the jaundice probably was due to intermittent obstruction of the common bile duct by a stone.

CLINICAL DIAGNOSIS: Metastatic carcinoma of the brain, primary site unknown.

#### PATHOLOGIC DISCUSSION

DR. FRANK A. TOWNSEND: At autopsy the primary tumor was found in the lower third of the esophagus. (Fig. 1.) It was a polypoid growth which partially filled the lumen; although it caused moderate dilatation,

\* PARSONS, R. J. and ZARAFONETIS, C. J. D. Histoplasmosis in man. *Arch. Int. Med.*, 75: 1, 1945.

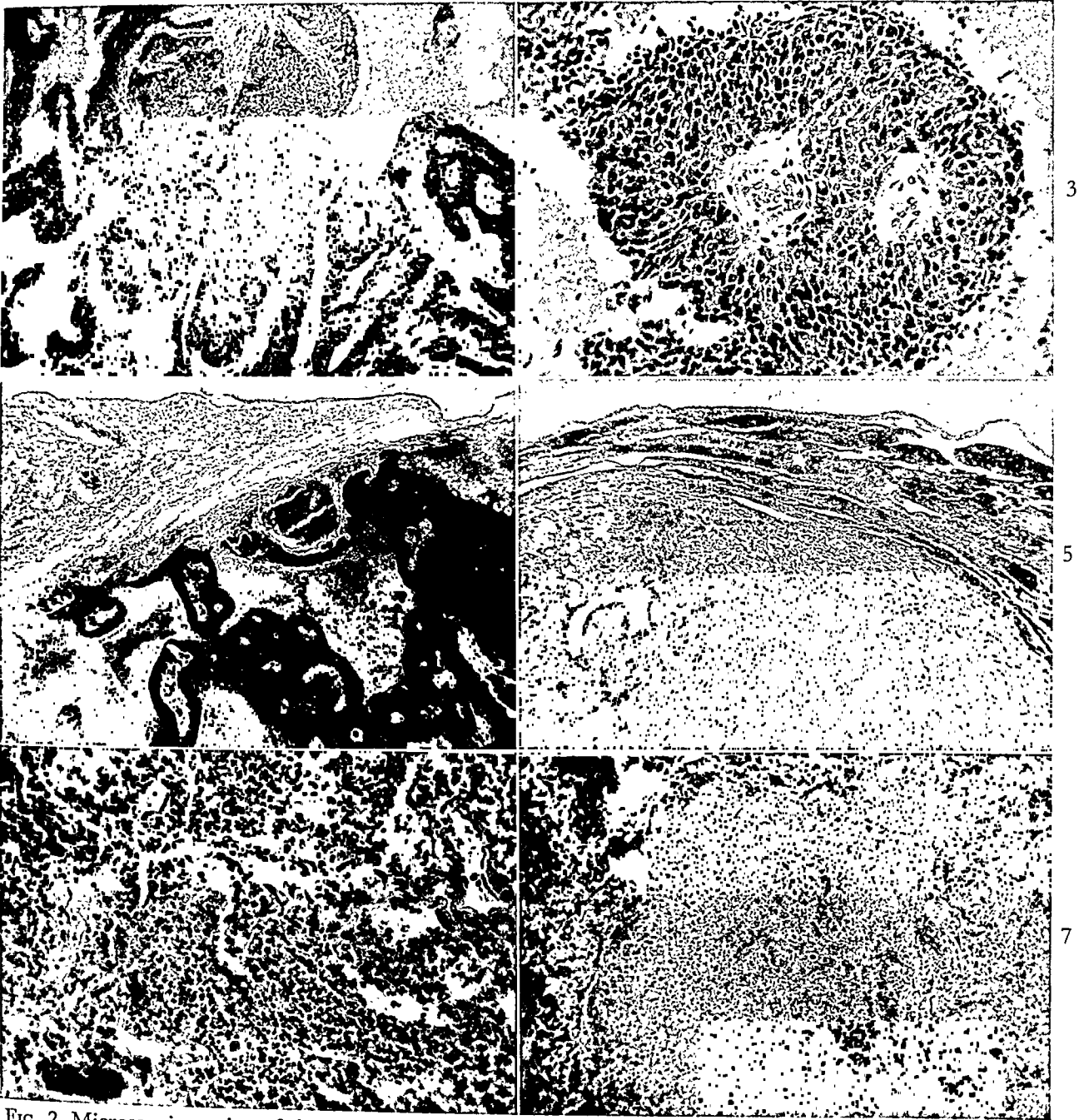


FIG. 2. Microscopic section of the esophageal tumor; note the absence of gland formation.

FIG. 3. High power view of the same section seen in Figure 2.

FIG. 4. Section of the metastatic nodule in the brain. Note the absence of tumor cells in the meninges.

FIG. 5. Section of the lymph node in the gastrohepatic omentum, showing carcinoma cells in the peripheral sinusoids.

FIG. 6. Section of the lung showing pneumonic exudate in the early stage of organization.

FIG. 7. Another section of the lung illustrating abscess formation. Note the infiltration by polymorphonuclear leukocytes.

there was no evidence of obstruction for the muscularis of the esophagus proximal to the tumor was not hypertrophied. In the right parietal region of the brain a tumor mass was found in the upper portion of the cere-

bral hemisphere just beneath the meninges. On cut section it appeared necrotic.

In addition, there were multiple abscesses in the lungs, measuring up to 2 cm. in diameter; these were associated with diffuse





FIG. 8. Section of a tracheobronchial lymph node illustrating one of the silicotic nodules.

bronchopneumonia involving all lobes of the lungs except the right middle lobe. The hilar lymph nodes were enlarged and firm and on section showed a marked degree of anthracosilicosis. There was advanced emphysema of the lungs. In addition, thrombi were present in the tertiary branches of the right pulmonary artery.

The liver was enlarged, weighing 1,850 Gm., and showed the changes of chronic passive congestion. The spleen, which was likewise enlarged, weighed 330 Gm. and contained much anthracotic pigment. Numerous small black stones, approximately 3 mm. in diameter, were found in the gallbladder but none were seen in the extrahepatic bile ducts. One node in the gastrohepatic omentum was large and firm. The cut surface bulged and was gray-white in color.

The heart was slightly enlarged weighing 420 Gm. The kidneys were normal in size but their surfaces were diffusely granular. These changes were interpreted as those of moderate arteriolar nephrosclerosis.

DR. R. A. MOORE: This patient had a primary carcinoma of the esophagus. The only demonstrable metastases were in the brain and in one lymph node of the gastrohepatic omentum. It was thus an unusual esophageal carcinoma in two respects. In the first place, there was no obstruction. The anatomic specimen confirmed the clini-

cal history which contained no reference to the signs or symptoms of esophageal obstruction. Secondly, the metastases were unusual in their distribution. The presence of a metastatic lymph node in the gastrohepatic omentum is uncommon for the usual lymph drainage of the esophagus is into the posterior mediastinum. Further, solitary metastases in the brain, without evidence of metastases in other organs, is an unusual postmortem finding.

Evidence of malaria, either grossly or microscopically, was lacking. There was no increase in the reticulo-endothelial cells or in the amount of pigment in the spleen. In regard to the several episodes of jaundice noted during the patient's hospital stay, it can be said that the patient did have chronic cholecystitis and cholelithiasis. The calcium bilirubinate stones in the gallbladder suggest the possibility that on several occasions a stone had passed into the common bile duct and given rise to transient obstruction.

On section the hilar lymph nodes contained only a small amount of calcium, much less than would have been suggested by the degree of radio-opaqueness they exhibited on the x-ray film of the chest. Dr. Goldman suggested the possibility of silicosis and on the basis of the gross examination, it seems likely that silicotic pigment rather than calcium was responsible for the roentgenologic appearance of the nodes.

Turning to the microscopic sections, Figure 2 shows a characteristic section of the esophageal tumor. The cells are seen to be epithelial in type and show no glandular pattern, but foci of necrosis are present. The appearance is that of an epidermoid carcinoma, the type which constitutes approximately 90 per cent of the malignant tumors of the esophagus. A high power view of the same section (Fig. 3) confirms the diagnosis of epidermoid carcinoma. In the gross, the tumor was somewhat unusual for

it was almost entirely encapsulated. Most esophageal tumors of a comparable size undergo ulceration.

In Figure 4 a section of the cerebral metastasis is seen and shows the tumor to be of an identical cellular type. Although the metastatic nodule has extended to the meninges, no tumor cells are present in the meninges themselves. This type of tumor rarely disseminates diffusely through the subarachnoid space. Figure 5 is a section of the lymph node in the gastrohepatic omentum; in the peripheral sinusoids of the node the same cell type is again seen.

A section of the lung (Fig. 6) is illustrative of the characteristic exudate of a pneumonia in the early stage of organization. The proliferating fibroblasts are added evidence that the pneumonia has been present for some time. In Figure 7 there is liquefaction and abscess formation; the abscesses vary from 1 mm. to 2 cm. in diameter. The pulmonary epithelium is completely de-

stroyed and is replaced by a fibrinous exudate which is infiltrated with polymorphonuclear leukocytes. The last section (Fig. 8) is a section of a tracheobronchial lymph node and shows the typical characteristics of a silicotic nodule.

DR. ALEXANDER: Do you believe that the proximity of the esophagus to the vertebral veins suggests that the cerebral metastases arose via that route?

DR. R. A. MOORE: That seems very likely but cannot be proven.

*Final Anatomic Diagnosis:* Epidermoid carcinoma of the esophagus with metastases to the brain and gastrohepatic lymph node; multiple abscesses of the lung; bronchopneumonia of the lung; thrombi of tertiary branches of the right pulmonary artery; arteriolar nephrosclerosis, moderate; anthracosilicosis of the lungs, tracheobronchial, bronchopulmonary, diaphragmatic, portahepatic, and retroperitoneal lymph nodes, and the spleen.

# Western Society for Clinical Research

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Treatment of Rheumatoid Arthritis with Massive Doses of Salicylates. . . V. B. JAGER

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## Electrocardiographic Patterns of Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads\*

MAURICE SOKOLOW, M.D. *and (by invitation)*  
THOMAS P. LYON, M.D.

**U**NIPOLAR precordial and limb leads, with the use of Wilson's or Goldberger's central terminal, have clarified and extended our knowledge of electrocardiography. In the present study, the detailed patterns of right and left ventricular hypertrophy were determined by the use of unipolar leads and the findings correlated with the typical patterns obtained by the standard limb leads. One hundred cases of left ventricular hypertrophy and fifty cases of right ventricular hypertrophy were studied.

The pattern of left ventricular hypertrophy varied depending on the degree of hypertrophy and the presence of associated coronary disease. Not all the abnormalities characteristic of left ventricular hypertrophy were present in every case; in some cases only a single typical abnormality was present. The findings most commonly seen in left ventricular hypertrophy were (1) depression of the S-T intervals with a low, diphasic or inverted T wave in the left precordial leads; (2) a delayed onset of the intrinsic deflection (greater than 0.05 second) in the left precordial leads, especially  $V_5$ ; (3) depression of the S-T interval with a low, diphasic or inverted T wave in lead  $aV_L$  in horizontal hearts (Wilson's criteria) and in lead  $aV_F$  in vertical hearts; (4) increased voltage R in left precordial leads and S in right precordial leads so as to present an R/S ratio smaller than normal in  $V_1$  and an R/S ratio greater than normal in  $V_5$ .

The unipolar limb leads not infrequently were the only leads demonstrating significant abnormality. Lead  $aV_L$  frequently was more abnormal than lead I and on occasion presented abnormal ST-T changes when lead I was normal. In vertical hearts abnormal ST-T changes were noted on occasion in  $aV_F$  with normal or equivocal findings in leads II and III. In advanced

\* From the Department of Medicine, University of California Medical School, San Francisco, Calif.

cases, abnormal T waves were seen in  $aV_L$ ,  $aV_F$  and  $aV_R$  with the last being characterized by an upright T wave. The ST-T changes, in general, were more frequent and more characteristic than was delayed onset of the intrinsic deflection. In many patients with left ventricular hypertrophy, confirmed by roentgenologic examination, left precordial leads did not show a delayed intrinsic deflection. On occasion, however, such delay was the only abnormal finding, and so of definite value.

Right ventricular hypertrophy was characterized by the following, not all of which need be present in every case: (1) a prominent, often tall R wave with an absent or minimal S wave in  $V_1$  and/or  $V_2$ ; (2) an abnormally great R/S ratio in  $V_1$  and/or  $V_2$ ; (3) a small R wave with a deep or prominent S wave in  $V_5$  and/or  $V_6$ ; (4) an abnormally small R/S ratio in  $V_5$  and/or  $V_6$ ; (5) delayed onset of the intrinsic deflection in  $V_1$  (more than 0.03 second); (6) prominent R wave in lead  $aV_R$ ; (7) depression of the S-T segment and inversion of the T waves in  $V_1$  and/or  $V_2$ ; (8) abnormal T waves in  $aV_L$  and/or  $aV_F$ , depending on the position of the heart.

The abnormalities seen in right ventricular hypertrophy are most typical in such diseases as tetralogy of Fallot. In chronic cor pulmonale associated with pulmonary fibrosis, emphysema, etc., the abnormalities are less marked and usually consist of small R waves and deep S waves with an abnormally small R/S ratio in  $V_5$ . The changes in  $V_1$  are less frequently seen, in contrast with tetralogy of Fallot when  $V_1$  is almost invariably abnormal.

The importance of  $V_1$  is stressed, since the abnormalities in this lead may be the major ones. Precordial leads  $V_2$ ,  $V_4$  and  $V_5$  may not be conclusive.

## Immunization of Human Beings with Group A Hemolytic Streptococci\*

LOWELL A. RANTZ, M.D.

**W**ASHED broth cultures of strains of group A hemolytic streptococci of types 3 and 17 that had been

\* From the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

demonstrated to produce large amounts of acid extractable, type specific protein, were heat killed and preserved with formalin. These were then injected subcutaneously in varying amounts into human beings at approximately weekly intervals for nine weeks. Serum was collected from each patient before the experiment and again four and ten weeks later. The presence of type specific antibodies was determined by the Rothbard technic. Precipitin tests using a non-type specific non-carbohydrate antigen present in acid extracts of group A hemolytic streptococci were also carried out.

Two subjects received vaccine of type 3, and two of type 17 equivalent to .37 mg. or more of bacterial N. Type specific antibodies appeared in all. The administration of the type 17 vaccine in amounts from .09 to .19 mg. N to three persons failed to stimulate the formation of measurable antibody. A similar range of dosage of type 3 vaccine was administered to four persons, one of whom developed type specific antibodies.

The results following immunization with the two types were similar with respect to the stimulation of precipitin formation. Four of seven of the study group who received the largest amounts of vaccine developed antibodies that reacted with substances contained in purified acid extracts of streptococcal cells. This antibody was present in four other individuals before immunization was begun. That it was not anti-"M" antibody is demonstrated by the fact that precipitation occurred with materials obtained from several different serological types.

Highly purified group carbohydrates prepared by Fuller's method and tested in suitable dilutions failed to induce precipitation with any serum obtained from ten subjects. In the eleventh, a reaction was obtained with both early and late sera.

In another similar study, thirty-two subjects received type 17 vaccine equivalent to .006 to .204 mg. N in three to five injections at weekly intervals. No antibodies of any kind developed in these persons.

The vaccines produced severe local reactions characterized by erythema and subcutaneous nodule formation in many persons. Striking differences existed in the amount of vaccine ac-

cepted by various subjects. Certain individuals who were able initially to accept large doses of vaccine without difficulty later reacted violently to similar or much smaller quantities of the antigen. This is believed to represent artificially induced hypersensitivity to group A hemolytic streptococci in man.

### Effects of Acute Anoxia on the Capillary Permeability of the Human Arm\*

J. P. HENRY, M.B., J. GOODMAN, PH.D. and J. P. MEEHAN

THE cuff technic of Landis et al. (*J. Clin. Investigation*, 11: 717, 1932) was employed to study the effects of anoxia on capillary permeability. Preliminary experiments were made to determine whether consecutive applications of congestion would give consistent results. Four subjects were submitted at sea level to thirty minutes of venous congestion (60 mm. Hg) twice repeated, with a rest period of sixty minutes between experiments. Duplicate hematocrit, hemoglobin and plasma protein estimations were made on blood samples from both control and congested arms. The mean fluid loss found in six such double experiments was in the first experiment  $5.8 \pm 0.5$  cc. and in the second  $6.3 \pm 0.6$  cc.

In a second series, one of the two consecutive experiments was run at a simulated altitude such that the oximeter reading was 65 to 75 per cent hemoglobin saturation. The mean estimated fluid loss for ten experiments at altitude was  $5.0 \pm 0.8$  cc. The corresponding sea level value for this experimental series was  $5.4 \pm 0.8$  cc. Analysis of the standard error of the fluid loss results shows that there is less than 1 chance in 100 that the loss at sea level differs by more than 20 per cent from that at altitude, with degrees of arterial hemoglobin saturation of the order of 70 per cent.

In addition, a number of double experiments were carried out using an injection of adrenalin in peanut oil in one of the tests as a means of raising the blood pressure for the thirty-minute

\* From the Department of Aviation Medicine, The University of Southern California School of Medicine, Los Angeles, Calif.

period of congestion. The fluid loss decreased very greatly when there was a marked rise, i.e., 20 to 30 mm. Hg in the blood pressure. This might explain the sharp decrease in fluid loss sometimes observed with severe anoxia, since in acute anoxia the blood pressure may increase by this amount.

### Effect of Local Cooling on Fluid Movement in the Human Forearm\*

ELLEN BROWN, M.D., CHARLES S. WISE, M.D.  
and EDWIN O. WHEELER, M.D.

**T**HE pressure plethysmograph was used to study the effect of cold on capillary permeability in man. The volume of a segment of forearm could be measured during application of a pressure of 200 mm. Hg to the water within the plethysmograph so that changes in extravascular fluid content, exclusive of vascular volume, were determined. Readings were made during application of pressure for two-minute periods which were separated by intervals of eight minutes. At plethysmograph temperatures of 34°, 24°, 14° and 4°c., "reduced arm volume" was measured in four normal subjects at ten-minute intervals (1) under resting conditions and (2) before and after raising venous pressure 20, 40 or 60 cm. water above resting level.

In order that venous pressure and initial tissue pressure might be as uniform as possible, the mid-point of the forearm segment was level with the manubrium sterni and the subject was prepared by a ninety-minute period of recumbency during which the arm was supported in this position. Even when these precautions were taken, there was a slight progressive decrease in reduced arm volume averaging .008 cc. per 100 cc. of arm per minute during eighty-minute observation periods at 34°c. This was related to the number of readings and not to elapsed time and was thought to be due to squeezing out of soft tissues by the pressure.

At temperatures below 34°c., reduced arm volume decreased less rapidly or actually increased. In every subject, a relative increase was apparent at 24°c. and swelling was successively

\* From the Department of Physiology, Harvard Medical School, Boston, Mass.

greater at 14° and 4°c. The average net increase in volume after sixty minutes at 4°c. was 1.03 cc. per 100 cc.

To determine the rate of filtration of fluid per unit rise of venous pressure, reduced arm volume was measured before and immediately after ten-minute periods of venous congestion. At 34°c. the average increase in volume per cm. rise in venous pressure was .0027 cc. per 100 cc. per minute. At 4°c. the unit filtration rate was reduced more than 30 per cent. After release of congestion, the rate of reabsorption per cc. of accumulated excess tissue fluid was less at 24°c. or below than at 34°c. In some instances at 4°c., there was no recovery and the arm continued to swell.

The increase in extravascular volume at constant venous pressure and impairment in reabsorption of excess tissue fluid found during cooling are most readily attributed to cellular injury with increased permeability of the capillary walls to protein and consequent reduction in effective osmotic pressure of the blood. Absolute proof of the presence of protein in the capillary filtrate is lacking and other factors must be considered. Even in the least sensitive subjects, abnormalities of fluid movement appeared at plethysmograph temperatures as high as 24°c. The decrease in unit rate of filtration observed during local cooling may be the result of (1) increased tissue pressure from edema fluid formed in the cold before congestion was begun, or (2) reduction in total area of capillary wall available for filtration.

### A Survey of Commercial Rh Antisera\*

O. B. PRATT, M.D.

**A** SURVEY of the blood grouping characteristics of all pregnant women on the obstetrical service of the White Memorial Hospital and clinic led to difficulty in obtaining sufficient Rh typing serum. When serum from various manufacturers was used, certain inconsistencies soon became apparent. A comparative study of all available commercial Rh typing sera was undertaken.

Six different antisera from four different manufacturers were tested on a total of 1,099

\* From the Institute of Experimental Medicine, College of Medical Evangelists, Los Angeles, Calif.

bloods from patients. One antiserum was produced in guinea pigs; all others were antisera of human origin. All tests were run according to the instructions of the manufacturer. Tests were read macroscopically and microscopically before and after centrifuging at 1,000 r.p.m.

The guinea pig serum gave positive reactions in all infants up to one month of age. This is in accordance with findings first reported by Fisk and Foord. This same guinea pig serum gave 85.7 per cent positives in the adult series. The antisera of human origin gave 88.7, 88.0, 80.2, 27.3, 44.7 and 10.0 per cent positive reactions, respectively. The last two observations listed were of tests on the same antiserum, the former using concentrated and the latter diluted antiserum according to the instructions of the manufacturer. Those antisera giving nearest 85 per cent positives showed certain inconsistencies, each giving some negative reactions with bloods which were positive with others. Titrations by the standard test tube method gave results varying from 1:4 to 1:32. All antisera were used within the expiration date set by the manufacturer.

Variations reported here may be due wholly or in part to variations in initial strength of the serum, deterioration of serum and failure to recognize the Rh subgroups in labeling the antisera. Slight variations in technic invariably lead to inconsistencies in the results of Rh typing procedures.

This study emphasizes the need of some central control of the standardization, assay and labeling of Rh testing antisera. Such control together with a standard technic should largely eliminate the conflicting results now encountered in Rh testing with commercial antisera.

### Effects of Dibenamine (Dibenzyl-beta-chloroethyl amine) on Human Subjects (Preliminary Report) \*

HANS H. HECHT, M.D., ROSCOE B. ANDERSON, M.D. and FERNE S. FOCHT, M.D.

**A**SERIES of tertiary amines, structurally related to nitrogen mustards (bis- or tris-chloroethyl-amines) has recently been

\* From the Medical Department, University of Utah Medical School, Salt Lake City, Utah.

introduced with the claim that compounds of this structure would block or reverse certain excitatory adrenergic responses in animals ("sympatholytic" action). One of these agents, dibenzyl-beta-chloroethyl amine ("Dibenamine") was made available to us for clinical trial and has been administered to fifty-four patients.

Intravenous administration was found to be the only route which was safe and which gave consistent and predictable results. The dose which can be tolerated appears to be 4 to 6 mg/kg., which is only one-fifth of the dose usually employed in animal experiments. A detailed study of the effect of this agent on the activity of the sympathetic nervous system was made in thirty-five patients who received a total of sixty-two injections.

In these patients and in the doses given, dibenamine appeared to block certain manifestations which occur upon the administration of epinephrine or other sympathomimetic compounds. Among those for which complete protection was afforded were (1) pupillary dilatation in dim light; (2) rise in arterial pressure induced by sympathomimetic compounds; (3) rise in venous pressure; (4) reflex (vagal) bradycardia with the development of independent ventricular rhythms and (5) reflex (vagal) changes of the T waves. In almost all instances postural reflexes were inhibited and pronounced orthostatic hypotension with positive Flack test developed. The blocking effect lasted for about twenty-four hours, rarely longer. An incomplete inhibition of sweat secretion was observed and the incidence and number of ectopic cardiac foci, readily induced by injection of epinephrine, could be reduced but not abolished. Dibenamine in the doses given failed to influence (1) rise in blood sugar; (2) rise in cardiac output; (3) capillary constriction; (4) tachycardia; and (5) depression of the S-T segment and lengthening of the Q-T interval. The resting arteriolar tone was not altered appreciably.

In doses that can be administered safely dibenamine appears to be an agent which prevents vasoconstriction and which may at times cause temporary vasodilatation. Certain other effects make it appear likely that compounds of this kind possess limited sympatholytic properties.



## Observations on Patients during Streptomycin Therapy\*

JOHN W. BROWN, M.D., HENRY D. BRAINERD, M.D., ROBERT W. OBLATH, M.D. and WILLIAM J. KERR, M.D.

**T**WENTY-SEVEN patients were treated with streptomycin. Each suffered from infection caused by an organism which was sensitive to streptomycin by *in vitro* test. These infections were as follows: (1) Systemic infections: These were brucellosis with bacteremia, typhoid fever, *H. influenzae* type b meningitis, *E. coli* and *Aerobacter aerogenes* sepsis and *A. aerogenes* endocarditis. (2) Urinary tract infections shown to be resistant to sulfonamides or in patients sensitive to these drugs. (3) Miscellaneous infections: These included one patient suffering from postoperative conjunctivitis and iritis caused by *Pseudomonas aeruginosa* in whom streptomycin was employed locally only and one patient with empyema and lung abscess in whom the predominant organism was *E. coli*.

The patients were studied throughout the course of infection, repeated cultures were made and the organisms tested for sensitivity to streptomycin. The level of streptomycin in the blood was measured occasionally. An attempt was made to correlate the *in vitro* sensitivity of organisms and the development of resistance under treatment with cultural and clinical outcome. The effects of streptomycin, both toxic and therapeutic, were observed.

The observations suggested certain therapeutic results. One patient with bacteremic brucellosis appeared to respond and has maintained an uneventful convalescence without relapse for four months. He received 5 Gm. of streptomycin in 1,000 cc. of physiological saline solution per day by continuous intramuscular infusion for fourteen days. The response may have been due to his tolerance for a moderately large dose of streptomycin administered continuously for two weeks. Another patient with bacteremic brucellosis failed to improve and blood cultures remained positive. He developed a sharp febrile reaction with maculopapular eruption when

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administered 3 Gm. daily by the continuous method. The course of typhoid fever in two patients did not seem to be affected by therapy. Streptomycin appeared specifically effective in four cases of *H. influenzae* type b meningitis. One patient with subacute bacterial endocarditis due to *A. aerogenes* improved rapidly with streptomycin and remained well during a short period of observation.

Acute or chronic urinary tract infections due to *E. coli* or *A. aerogenes* responded quickly and showed little tendency to relapse when the urinary tract was structurally normal. In such circumstances the urine became sterile within a few hours, even when several million organisms per cc. of urine were present before treatment. When structural abnormalities were present, however, recurrence of infection occurred. At this time the resistance of the organisms to streptomycin was found to be increased many fold. *Pseudomonas aeruginosa* became resistant very quickly and recurrence developed more frequently when it was the infecting organism.

Streptomycin was given by continuous intramuscular infusion, intermittent intramuscular injection, intraspinally and intrapleurally. Only two significant reactions were encountered. Fever and eruption occurred in one patient and mild temporary ataxia in another. Both patients suffered from brucellosis and both received streptomycin by continuous intramuscular injection.

## Mechanism of the Development of Resistance to Streptomycin\*

HENRY K. SILVER, M.D. and C. HENRY KEMPE, M.D.

**T**HE development of resistance to streptomycin is of practical as well as theoretical importance, since it has been observed that resistant strains of pathogenic organisms develop with relative frequency after treatment with streptomycin. The exact mechanism of the development of resistance has not been determined, but it has been postulated that resistant strains of an organism might be found after exposure to some antibacterial agent

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because the organisms were: (1) naturally resistant; (2) rendered resistant by contact with an antibacterial substance; (3) obtained by natural selection; or (4) in an insusceptible phase at the time of exposure.

In studying the mechanism of the development of resistance of micro-organisms to streptomycin the method of testing was based on the twenty-four hour inhibition of growth of the organism when fertile hens' eggs were used as the culture medium. Using this method bacterial suspensions of colony mixtures of a single strain of *Escherichia coli* were found to be inhibited by 5 micrograms of streptomycin per chick embryo. The mixed suspension then was cultured on agar plates and 100 individual colonies were tested for their sensitivity to streptomycin. It was found that there was a marked variation of the sensitivities of the individual colonies. Although 62 per cent of the colonies were sensitive to between 2 and 8 micrograms of streptomycin per fertile egg, it was found that the most resistant colonies required over 100 times as much streptomycin as the most sensitive ones even though they were all isolated from the same strain. When the results of the sensitivity tests were plotted, they formed a standard curve of distribution. Similar distribution was noted when the individual components making up a resistant strain of *E. coli* were tested for their sensitivity to streptomycin. None of the organisms tested in these experiments had had any previous exposure to streptomycin and any resistance that was demonstrated was a natural characteristic of that particular component and had not been influenced by contact with the antibiotic.

These results support the theory that even sensitive strains of an organism originally contain resistant components. It was found that the sensitivities of the individual components of any organism formed a curve of distribution if these sensitivities are plotted. It is suggested that suspensions of colony mixtures rather than individual colonies should be used for tests of sensitivity to streptomycin in order to avoid the inadvertent testing of either extreme in the range of sensitivities of the various individual components, so that the average sensitiveness of the strain tested can be determined.

## Plasma Angiotonase Concentration in Normal and Toxemic Pregnancies\*

ERNEST W. PAGE, M.D.

**A**NGIOTONASE is the term applied to that component of the renal pressor system capable of inactivating angiotonin. Despite the widespread distribution and high activity of angiotonase in various tissues, we have shown that only the small amount of enzyme which is free in the plasma is normally available for angiotonin destruction. If the "deficiency theory" of human hypertension accounted for the elevation of blood pressure in eclampsia, reduced plasma concentrations of angiotonase should be encountered in that disease.

A method based upon the kinetics of angiotonase activity has been applied to the measurement of plasma concentration in ten healthy non-pregnant subjects, sixteen normal pregnancies and ten cases of pre-eclampsia or eclampsia. In normal pregnancy, there is a four to eightfold increase in angiotonase activity. In eclampsia, there is a wider range of concentrations, but no correlation between the enzyme level and the degree of hypertension.

If plasma angiotonase is the primary means by which circulating angiotonin is destroyed, it would be anticipated that pregnant women would respond to intravenously injected angiotonin with a blood pressure rise of relatively short duration. This was tested and found to be true.

It is concluded that a deficiency of angiotonase is not the cause of the hypertension in eclampsia.

## Relation of the Distribution of Crash Injuries in Man to Those Observed in Animals during Experimental Deceleration†

ROBERT F. RUSHMER, M.D.

**I**N the past, information concerning the nature and characteristics of desirable protective devices and the methods of

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treating internal injuries of various types has been obtained largely by studies of accidents and their victims. During the recent war, a series of experiments was conducted on experimental animals (anesthetized cats) exposed to sudden deceleration under controlled conditions to determine if the nature of the injuries produced bore any relation to those observed in humans coming to autopsy following aircraft accidents.

It was noted that lesions in the lungs predominated in both humans and animals and were characterized by profuse interstitial hemorrhages, the distribution of which did not appear to bear any particular relation to the direction of action of the force. In humans, traumatic emphysematous areas were quite frequently found and were occasionally seen in the animals. Lacerations and herniation of the diaphragm were encountered in both series. Lacerations of the capsule of the liver and spleen and extending into the parenchyma were characteristic findings in both man and cat.

Traumatic lesions in the brain, heart, gastrointestinal tract and skeleton were frequently encountered in humans but could rarely be produced in the animals under the conditions obtaining in the experiments. In no case was the severity of these injuries comparable to those produced in humans. This was attributed to the fact that the velocity at impact, the duration of the force and the mass and degree of relaxation of the body of the animals were markedly different than those encountered in aircraft accidents.

The evidence presented indicated that, given sufficient velocity at impact, the lesions which are so frequently observed in any type of exposure to force may be reproduced in animals with sufficient accuracy to allow investigation of means of protection and method of treatment.

### Serologic Reactions in Trichinosis\*

ARTHUR W. FRISCH, M.D.

**A**N epidemic of mild trichinosis among a large group of prisoners of war offered an unusual opportunity to study the

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serologic response to the disease under relatively controlled conditions. A total of 250 cases were followed during the acute phase, three, six, and twelve weeks later by means of intradermal, precipitin and complement fixation tests. Positive immediate skin responses were obtained in 42 to 50 per cent of patients using an alkaline saline extract of trichina larvae which had been placed in boiling water to remove heat precipitable material. Antigens prepared by the methods commonly employed differed markedly in activity from each other and lacked sensitivity. The maximal incidence of positive complement fixation reactions was 37 per cent whereas the highest value of the precipitin test never exceeded 6 per cent. As a result of the experience gained, a re-evaluation of serologic procedures for the diagnosis of trichinosis appears to be necessary.

Additional studies with purified extracts in the form of an acid soluble protein and a polysaccharide revealed that they did not constitute the active component. The fraction of trichina larvae responsible for complement fixation proved to be heat stable and precipitable with acetone and alcohol. On the basis of these findings a practical approach to the problem of obtaining standardized trichina extracts is presented.

### Collateral Circulation of the Normal Human Heart\*

MYRON PRINZMETAL, M.D., BENJAMIN SIMKIN, M.D., H. C. BERGMAN, PH.D. and H. E. KRUGER

**T**HE collateral circulation in the normal human heart has been examined by the use of technics previously not reported: (1) perfusion of the coronary vessels with human radioactive red cells to determine the presence of anastomotic channels, and (2) an injection mass containing glass spheres of varying diameter to determine the size of such anastomotic channels.

Human erythrocytes made radioactive by incubation with radiophosphorus ( $P^{32}$ ) were perfused through either the anterior descending

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or circumflex branch of the left coronary artery and the distribution of erythrocytes was determined by means of (1) Geiger counts at arbitrarily chosen areas on the pericardial and endocardial surfaces, and (2) radio-autographs of the unrolled heart. Abundant amounts of the labelled erythrocytes were found throughout the left ventricle, indicating numerous anastomoses within the left ventricle; and some radioactivity was present in the vascular tree of the right ventricle, confirming the existence of anastomotic channels between the right and left ventricles.

Glass spheres 10 to 440 micra in diameter were suspended in a radiopaque gelatin mixture, perfused through one of the coronary arteries of normal human hearts (four to seventy-three years of age) at physiologic pressures, and collected from the opposite coronary artery, the coronary sinus and the ventricular cavities. Spheres of 70 to 180 micra in diameter were recovered from the opposite coronary artery, 70 to 170 micra from the coronary sinus and 70 to 220 from the ventricular cavities. These findings indicate the existence of intercoronary anastomoses of arteriolar dimensions in the normal human heart. Also the presence of arteriovenous anastomoses is demonstrated. In preliminary studies in coronary arteriosclerosis and ventricular hypertrophy, glass spheres of 120 to 150 micra were recovered from the opposite coronary vessel.

### Alterations in the Arterial Pulse Wave in Patients with Cardiovascular Disease\*

GEORGE S. EDWARDS, M.D.

(Introduced by R. Drury)

IT was noted during an investigation of blood pressure determinations with a recording oscillometer that there were considerable variations in the configuration of the arterial pulse wave. Investigation of these changes were undertaken. Initially a purely mechanical recording device (sphygmoscope) was utilized. Even with such a relatively insensitive instrument, characteristic wave patterns were found

in certain specific pathological conditions. Sufficient data were obtained to make continuation of the problem seem desirable. To this end a far more sensitive instrument was developed which incorporated a differential chamber and optical recording system.

Cases studied included examples of coarctation of the aorta, patent ductus arteriosus, traumatic occlusion of the terminal aorta, congenital enlargement of the brachial artery, calcific aortic stenosis, aneurysms of the aortic arch, aortic regurgitation, postural hypotension, malignant hypertension, occlusive vascular disease in diabetics and non-diabetics, and a large number of instances of hypertensive and arteriosclerotic cardiovascular disease and instances of rheumatic heart disease with mitral and/or aortic lesions. In those cases in which autopsies were obtained, the predicted pathological condition was demonstrated.

It is believed that alterations in arterial wave form are an important diagnostic adjunct and have definite prognostic value in certain types of early cardiovascular disease.

In order to evaluate more critically the factors concerned in those pulse wave changes, refinements in instrumentation are being carried out. Further studies are under way which incorporate simultaneous recordings of direct and indirect arterial pulse waves at two or more points, together with venous pressure measurements and digital plethysmographs.

### Direct Measurement of Blood Pressure within Arterial Aneurysms and Arteriovenous Fistulas\*

NORMAN E. FREEMAN, M.D.

A METHOD is described for the direct measurement of pressures within arterial aneurysms and arteriovenous fistulas. A three-way stopcock is fitted with short lengths of rubber tubing connecting a No. 20 gauge needle with a 10 cc. syringe. To the third arm is attached an aneroid manometer similar to that used with a blood pressure cuff. The manometer is not sterile, but it is enclosed in a sterile transparent oiled silk cover.

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\* From the Department of Surgery, University of California Medical School, San Francisco, Calif.

The blood pressure within aneurysmal sacs was measured at the time of operation in twelve patients with arterial aneurysms and eleven patients with arteriovenous fistulas. The mean initial pressure in the group with the arterial aneurysms averaged 84 mm. of Hg, with variations between 110 and 34 mm. of Hg. Upon constriction of the afferent artery the pressure fell to an average of 58 mm. of Hg. In the patients with arteriovenous fistulas the mean initial pressure averaged 40 mm. of Hg with variations between 70 and 30 mm. of Hg. With constriction of the afferent artery the pressure fell to an average of 10 mm. of Hg.

Determination of the intra-aneurysmal pressure following temporary occlusion of the component vessels has been found useful not only in estimating the degree of development of collateral circulation but also in disclosing the presence of unsuspected collateral vessels which empty into the aneurysmal sac and which have to be controlled before the aneurysm can be safely opened.

The lowest mean arterial pressure found after excision of an aneurysm or arteriovenous fistula was 32 mm. of Hg. With pressures at or above this level, adequate circulation of blood to the peripheral tissues while at rest has been observed in these patients. However, although no case of gangrene was observed with such low pressures, there was evidence of impaired circulation in two patients, as shown by absent pulses and increased fatigue following muscular activity.

## Diagnosis of Pancreatic Disease by Enzyme Tests\*

LESTER M. MORRISON, M.D.

**O**VER 1,000 pancreatic enzyme tests were made on the duodenal secretions in a group of normal subjects, a group of patients with "functional" or non-organic disease of the upper digestive tract and a group of patients with organic disease of the pancreas, biliary tract, stomach or duodenum.

The range and mean of duodenal pancreatic enzyme tests for normal subjects and patients

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suffering from upper digestive tract disorders is described. A recent method of estimating pancreatic enzymes, introduced by Free, Beams and Myers is employed and substantiated in this series of cases.

The findings in a group of ten patients with chronic, low-grade or moderate inflammation of the pancreas as revealed at operation are recorded. The duodenal enzyme studies in these cases failed to show any consistently abnormal findings of diagnostic value, either before or after operation.

Normal subjects as well as patients with extensive and severe pathological involvement of the pancreas like cancer may give zero or near zero test readings in individual duodenal pancreatic enzyme tests.

In patients with organic disease of the stomach or biliary tract, pancreatic duodenal enzyme tests revealed no individual distinctive or diagnostic findings. However, their group mean value was definitely lower than the comparable value in normal subjects.

In six cases of extensive involvement of the pancreas by cancer, or cirrhosis with pancreatic lithiasis, 125 tests gave abnormal findings in the duodenal pancreatic enzyme tests. These abnormal findings were either zero or near zero values.

If a zero reading was found in the pancreatic enzyme tests of a normal subject, it was not consistently found in all subsequent determinations.

In the presence of advanced and extensive pancreatic disease such as cancer or cirrhosis, zero or near zero readings were found consistently in all subsequent determinations.

## Treatment of Rheumatoid Arthritis with Massive Doses of Salicylates—with Particular Reference to Modification of Plasma Protein Constituents during Therapy\*

V. B. JAGER, M.D.

**A**BNORMALITIES of the blood frequently are observed in patients with rheumatoid arthritis. Often there is moderate anemia and an elevated erythrocyte sedimenta-

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tion rate. The plasma fibrinogen tends to be elevated. Frequently there is a moderate reduction in serum albumin and an increase in total serum globulin. The gamma globulin fraction, in particular, may be greatly elevated.

During the past eighteen months we have treated sixteen cases of rheumatoid arthritis with massive doses of salicylates. The clinical response occasionally was excellent; however, improvement usually was less striking and was partially offset by the unpleasant symptoms of salicylate intoxication. Anemia was found to disappear in those patients in whom this was present at the beginning of therapy. Changes in plasma fibrinogen and erythrocyte sedimentation rate during therapy were variable. Usually it was possible to demonstrate that during the course of salicylate therapy the initially low serum albumin returned to a normal value while the initially elevated serum globulin decreased toward normal values. Likewise the "gamma globulin" fraction of serum as determined chemically usually was greatly elevated prior to therapy and decreased during treatment with salicylates.

It was not possible to maintain desired plasma salicylate levels in every patient during therapy. It appeared, however, that return of these blood constituents to normal values occurred more frequently in those patients in whom high plasma salicylate levels could be maintained. With cessation of therapy, clinical relapses occurred frequently and the blood constituents tended to return to their pre-treatment values.

We do not imply that massive doses of salicylates constitute a superior form of therapy in the treatment of rheumatoid arthritis. Nevertheless the changes produced by salicylates deserve further study as regards the mechanism of production of arthritis as well as the mechanism of action of sodium salicylate.

## Hyperplasia of the Gastric Mucosa in Man\*

ALVIN J. COX, M.D.

A QUANTITATIVE study of 130 human stomachs obtained at autopsy soon after death has shown a broad range in the quantity of mucosal tissue. The quantitative difference is most pronounced in the specific secretory portion of the mucosa. An expression of the amount of acid secreting tissue in each stomach was obtained by estimating the total number of parietal cells. Fourteen cases of active or healed duodenal ulcer all had parietal cell numbers in the upper portion of the range, while nine cases of chronic gastric ulcer had no uniform distribution.

No constant relationship could be recognized between the amount of mucosal tissue and the degree of cellular infiltration, so it is concluded that hyperplasia and gastritis are manifestations of separate processes, and the term "hypertrophic gastritis" is misleading.

\* From the Department of Pathology, Stanford University School of Medicine, San Francisco, Calif.

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